N-ARYL-2-OXAZOLIDINONE-5-CARBOXAMIDES AND THEIR DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of United States Provisional Application Serial No., 60/428,025, filed, November 21, 2002, and United States Provisional Application Serial No., 60/445,530, filed, February 6, 2003, both of which are incorporated herein by reference in their entireties.

FIELD OF INVENTION

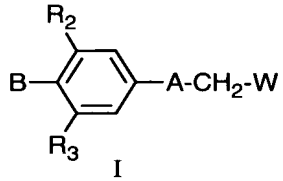
The present invention relates to novel N-Aryl-2-oxazolidinone-5-carboxamides, derivatives thereof, and their preparations. These compounds have potent antibacterial activity.

BACKGROUND OF THE INVENTION

The oxazolidinone antibacterial agents are a novel synthetic class of antimicrobials with potent activity against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium.*

SUMMARY OF THE INVENTION

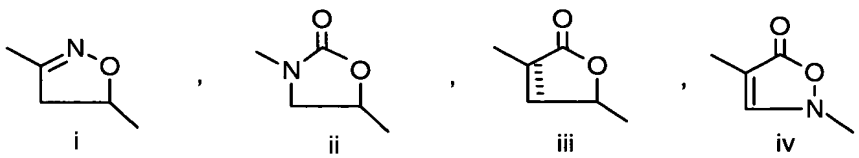
In one aspect, the invention features compounds of Formula I.



I

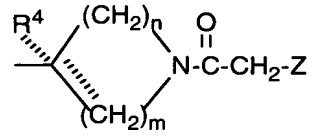
or pharmaceutically acceptable salts thereof wherein:

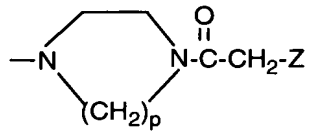
A is a structure i, ii, iii, or iv;



i ii iii iv

B is

(a) 

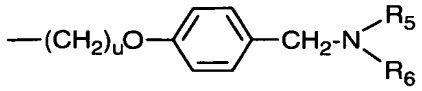
(b)  ;

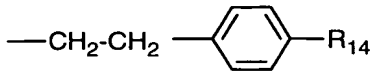
W is $-N(H)C(X)-R_1$, Het, or –Y-HET, in which the Het or –Y-HET is optionally substituted with =S or =O, provided that when A is structure iv, W is not –Y-HET or Het;

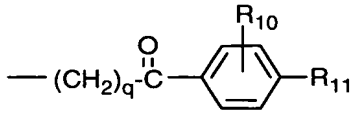
X is O or S;

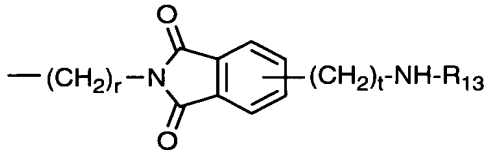
Y is NH, O, or S;

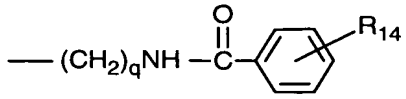
Z is

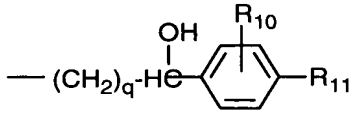
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

R_1 is a) H,

b) NH_2,

c) NHC_{1-4}alkyl,

d) C_{1-4} alkyl,

e) C_{2-4} alkenyl,

f) O-C_{1-4} alkyl,

g) S-C_{1-4} alkyl, or

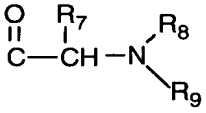
h) $(CH_2)_s$ C_{3-6} cycloalkyl, in which each occurrence of alkyl or cycloalkyl in R_1 is optionally substituted by one, two or three halogens (F or Cl);

Each R_2 and R_3 is independently hydrogen, halogen (F or Cl), methyl or ethyl;

R_4 is H, CH_3 or F;

R_5 is H or C_{1-4} alkyl;

R_6 is H, C_{1-4} alkyl, or



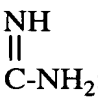
;

or R_5 and R_6 together form an optionally substituted saturated heterocycle;

R_7 is H, or C_{1-4} alkyl which can be optionally substituted by -OH, $-NH_2$, -NH-C(=NH)-NH_2, -SH, $-SCH_3$, -COOH, $-C(O)NH_2$, phenyl which can be optionally substituted with –OH;

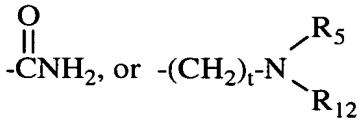
R_8 is H or CH_3;

R_9 is H, CH_3, $-C(O)-CH(R_7)-NR_8R_8$,

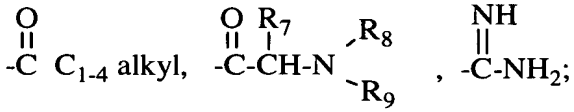


;

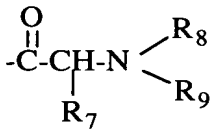
R_{10} or R_{11} is halo, C_{1-4}alkyl, CF_3, -CN, $-NO_2$, -OH, -O-C_{1-4}alkyl, -NH-$S(O)_wC_{1-4}$alkyl;



R_{12} is H, C_{1-4} alkyl, $-S(O)_2-C_{1-4}$alkyl,



or R_5 and R_{12} together form a saturated heterocycle;

R_{13} is H, or  ;

R_{14} is $-(CH_2)_tNHR_{13}$, -OH, $-OC_{1-4}$alkyl;

m is 0, 1, 2, 3, 4;

n is 0, 1, 2, 3, 4 with the proviso that m plus n is 2, 3, 4, or 5;

p is 2, 3;

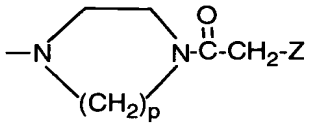
q is 1, 2;

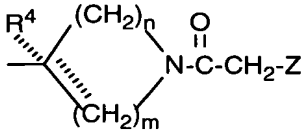
r, s and t are independently 0, 1;

u and w are independently 0, 1, 2; and

provided that W is not Het or –Y-HET when Z is a, b, or d, and further provided that Z is not b when A is formula iii.

Embodiments of the invention may have one or more of the following. R_{10} is CF_3. R_{11} is CF_3. Heterocycle is piperidino, pyrrolidino, morpholino, thiomorpholino, or 4-methyl-1-piperazinyl. Het is a triazole or a tetrazole. B is

(b)  . p is 2. B is

(a)  . n and m are both 2. n and m are both 1. R_4 is –CH_3. Z is (a). R_5 and R_6 are C_{1-4} alkyl. R_5 and R_6 together form an optionally substituted saturated heterocycle. R_5 and R_6 form an optionally substituted morpholinyl and piperazinyl. R_5 and R_6 form a morpholinyl and piperazinyl each of which are substituted with C_{1-4} alkyl. u = 0. Z is (c). R_{10} is H. R_{11} is $–C(O)-NH_2$, $-NHS(O)_uC_{1-4}$alkyl, or $–(CH_2)_t-NR_5R_{12}$. R_{11} is $–CH_2N(C_{1-4}alkyl)_2$, $–CH_2$-saturated heterocycle, $–CH_2-NH-C_{1-4}$alkyl, $–CH_2-N(C1-4alkyl)-C(O)-CHR_7-NR_8R_9$, $–CH_2-NH-C(O)-C_{1-4}$alkyl, $–CH_2-NH-SO_2-(C1-4alkyl)$, $–CH_2-NH_2$, or $-NH-C(O)-CHR_7-NR_8R_9$. R_{10} is ortho to R_{11}. q is 1. Z is (b). R_{14} is $–OC_{1-4}$ alkyl, -OH, or $-NH-C(O)-CH(R_7)-NR_8R_9$.

In another aspect, the invention features a method for the treatment of microbial infections in mammals by administering an effective amount of compound of formula I to a mammal. The compound may be administered to the mammal orally, parenterally, transdermally, or topically. The compound may be part of a pharmaceutical composition. The compound may be administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, e.g., from about 1 to about 50 mg/kg of body weight/day.

In another aspect, the invention features a pharmaceutical composition including a compound of claim 1 and a pharmaceutically acceptable carrier.

Specific compounds of the invention include:

N-[((5*S*)-3-{4-[4-({4-[(Diethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] propanethioamide.

N-[((5*S*)-3-{4-[4-({4-[(Diethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] cyclopropanecarbothioamide.

N-[((5*S*)-3-{4-[4-({4-[(Diethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.

N-[((5*S*)-3{4-[4-({4-[(Dimethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] propanethioamide.

N-[((5*S*)-3-{4-[4-({4-[(Dimethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] cyclopropanecarbothioamide.

N-[((5*S*)-3-{4-[4-({4-[(Dimethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.

N-({(5*S*)-3-[3-Fluoro-4-(4-{[4-(morpholin-4-ylmethyl)phenoxy] acetyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) propanethioamide.

N-({(5*S*)-3-[3-Fluoro-4-(4-{[4-(morpholin-4-ylmethyl)phenoxy] acetyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) cyclopropanecarbothioamide.

N-({(5*S*)-3-[3-Fluoro-4-(4-{[4-(morpholin-4-ylmethyl)phenoxy] acetyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

N-[((5*S*)-3-{3-Fluoro-4-[4-({4-[(4-methylpiperazin-1-yl)methyl] phenoxy}acetyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] propanethioamide.

N-[((5*S*)-3-{3-Fluoro-4-[4-({4-[(4-methylpiperazin-1-yl)methyl]phenoxy}acetyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide (38)

N-[((5*S*)-3-{3-Fluoro-4-[4-({4-[(4-methylpiperazin-1-yl)methyl]phenoxy}acetyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] acetamide.

N-[((5*S*)-3-{4-[4-(4-{4-[(Dimethylamino)methyl]phenyl}-4-oxobutanoyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide.

N-[((5*S*)-3-{4-[4-(4-{4-[(Dimethylamino)methyl]phenyl}-4-oxobutanoyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide.

N-[((5*S*)-3-{4-[4-(4-{4-[(Dimethylamino)methyl]phenyl}-4-oxobutanoyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.

N-({(5*S*)-3-[3-Fluoro-4-(4-{4-[4-(4-morpholinylmethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide.

N-({(5*S*)-3-[3-Fluoro-4-(4-{4-[4-(4-morpholinylmethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

N-({(5*S*)-3-[3-Fluoro-4-(4-{4-[4-(4-morpholinylmethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide.

N-[((5*S*)-3-{3-Fluoro-4-[4-(4-{4-[(methylamino)methyl]phenyl}-4-oxobutanoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.

N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-piperazin-1-yl]-4-oxobutanoyl}benzyl-N^1-methylglycinamide.

N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)-N^1,N^2,N^2-trimethylglycinamide.

N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)-N^2,N^2-dimethylglycinamide.

N^1-(4-{4-[4-[2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)-N^2,N^2-dimethylglycinamide.

(*S*)-N^1-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)alaninamide.

(*S*)-N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-2-oxobutanoyl}benzyl)alaninamide.

N^1-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)glycinamide.

(*S*)-Alanyl-(*S*)-N^1-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)alaninamide.

(*S*)-Alanyl-(*S*)-N^1-(4-{4-[4-(4-{(5*S*)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)alaninamide.

N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}benzyl)acetamide.

N-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutanoyl}benzyl)acetamide.

N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-{[(methylsulfonyl)amino]methyl}phenyl)-4-oxobutanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-{[(methylsulfonyl)amino]methyl}phenyl)-4-oxobutanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide.

N-({(5*S*)-3-[4-(4-{4-[4-(Aminomethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide.

N-({(5*S*)-3-[4-(4-{4-[4-(Aminomethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)glycinamide.

2-[3-methyl-3-(4-{(5S)-2-oxo-5-[(propionylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)azetidin-1-yl]-2-oxoethyl 4-(aminomethyl)benzamide.

N-{[(5S)-3-(4-{1-[4-(4-aminophenyl)-4-oxobutanoyl]-3-methylazetidin-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanamide.

N-({(5S)-3-[4-(1-{4-[4-(glycylamino)phenyl]-4-oxobutanoyl}-3-methylazetidin-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide.

N-{[(5S)-3-(4-{1-[4-(4-aminophenyl)-4-oxobutanoyl]-3-methylazetidin-3-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N~1~-(4-{4-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-methylazetidin-1-yl]-4-oxobutanoyl}phenyl)glycinamide.

2-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-methylazetidin-1-yl]-2-oxoethyl-4-(aminomethyl)benzamide.

N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-methoxyphenyl)butanoyl]piperazine-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-hydroxyphenyl)butanoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

2,2-Difluoro-N-{[(5*S*)-3-(3-fluoro-4-{4-[4-(4-methoxyphenyl)butanoyl] piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}ethanethioamide.

N-{[(5*S*)-3-(4-{4-[4-(4-Bromophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N-{[(5*S*)-3-(4-{4-[4-(4-Bromophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}ethanethioamide.

N-{[(5*S*)-3-(4-{4-[4-(4-Cyanophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}benzamide.

4-{4-[4-(4-{(5*S*)-5-[(Ethanethiolylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}benzamide.

N-{[(5*S*)-3-(4-{4-[4-(4-Chlorophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N-{[(5*S*)-3-(4-{4-[4-(4-chlorophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}ethanethioamide.

N-[((5*S*)-3-{3-Fluoro-4-[4-(4-{4-[(methylsulfonyl)amino]phenyl}-4-oxobutanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide.

N-[((5*S*)-3-{3-Fluoro-4-[4-(4-{4-[(methylsulfonyl)amino]phenyl}-4-oxobutanoyl-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide. N-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)acetamide.

2-Amino-N-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)acetamide.

N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)-2-aminoacetamide.

N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)-(2*S*)-2-aminopropanamide.

N-1-(4-{4-[4-(4-{(5*S*)-5-[(Ethanethiolylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}phenyl)-(*S*)-alaninamide.

N^1-[4-(5-{4-[4-((5*S*)-5-{[(2,2-Difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]piperazin-1-yl}-5-oxopentanoyl)phenyl]glycinamide.

N^1-(4-{5-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopentanoyl}phenyl)glycinamide.

N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutyl}phenyl)-2-aminoacetamide.

2-Amino-N-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutyl}phenyl)acetamide.

(*S*)-2-Amino-N-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutyl}phenyl)propanamide.

N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutyl)phenyl)-2-(dimethylamino)acetamide.

N-(4-{4-[4-(4-{(5*S*)-5-[(Ethanethiolylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutyl}phenyl)-2-(dimethylamino)acetamide

N^1-(3-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-1-hydroxy-4-oxobutyl}phenyl)glycinamide.

N^1-[3-(4-{4-[4-((5*S*)-5-{[(2,2-Difluoroethanethiolyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]piperazin-1-yl}-4-oxobutanoyl)phenyl]glycinamide.

N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(3-nitrophenyl)-4-oxobutanoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}actamide.

N^1-(3-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}phenyl)glycinamide.

N-{[(5*S*)-3-(4-{4-[4-(2-Aminophenyl)-4-oxobutanoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N-{[(5*S*)-3-(4-{4-[(5-Amino-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

N^1-(2-{2-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-2-oxoethyl}-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)glycinamide.

N^1-[2-(3-{4-[4-((5*S*)-5-{[(2,2-Difluoroethanethiolyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]piperazin-1-yl}-3-oxopropyl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl) glycinamide.

Compounds of Formula I have antibacterial activity against a number of human and veterinary pathogens including Gram-positive aerobic bacteria such as multiply-resistant-staphylococci, streptococci and enterococci, Gram-negative organisms such as *H. influenzae* and *M. catarrhalis*, anaerobic organisms such as Bacteroides spp. and *clostridia* spp., *Mycobacterium tuberculosis*, *M. avium* and *M.* spp. and in organisms such as *Mycoplasma* spp. For use as antibacterial agents the compounds of this invention can be administered orally or parenterally in a dosage range of about 0.1-100 mg/kg or preferably of about 1.0-50 mg/kg of body weight per day. Advantageously, the compound of the invention exhibit antibacterial activity against *S. aureus* resistant organisms.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used, unless otherwise described.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon

atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-7} alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The term "halo" refers to a halogen atom selected from Cl, Br, I, and F.

The term "alkyl" refers to both straight- and branched-chain moieties. Unless otherwise specifically stated alkyl moieties include between 1 and 6 carbon atoms.

The term "alkenyl" refers to both straight- and branched-chain moieties containing at least one –C=C–. Unless otherwise specifically stated alkenyl moieties include between 1 and 6 carbon atoms.

The term "alkoxy" refers to –O-alkyl groups.

The term "cycloalkyl" refers to a cyclic alkyl moiety. Unless otherwise specifically stated cycloalkyl moieties will include between 3 and 7 carbon atoms.

The term "amino" refers to $–NH_2$.

The term "aryl" refers to phenyl and naphthyl.

The term "het" refers to mono- or bicyclic ring systems containing at least one heteroatom selected from O, S, and N. Each monocyclic ring may be aromatic, saturated, or partially unsaturated. A bicyclic ring system may include a monocyclic ring containing at least one heteroatom fused with a cycloalkyl or aryl group. A bicyclic ring system may also include a monocyclic ring containing at least one heteroatom fused with another het, monocyclic ring system.

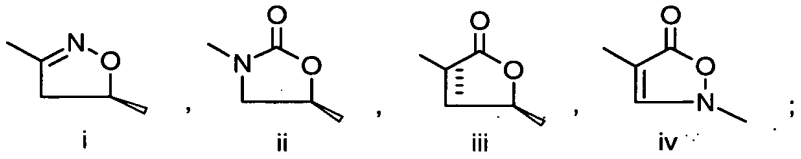
Examples of "het" include, but are not limited to, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 1,2,3-oxathiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, 5-methyl-1,3,4-

thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone, phthalimide, quinolinyl, morpholinyl, benzoxazoyl, diazinyl, triazinyl, quinolinyl, quinoxalinyl, naphthyridinyl, azetidinyl, pyrrolidinyl, hydantoinyl, oxathiolanyl, dioxolanyl, imidazolidinyl, and azabicyclo[2.2.1]heptyl.

The term "heterocycle" refers to a fully saturated het, examples of which include, but are not limited to, morpholinyl, thiomorpholinyl, and tertrahydropyranyl.

Specific R_3 and R_4 substituents include H, F, Cl, Br, CN, NH_2, NO_2, CH_3.

Specific structures of A include



Mammal refers to human or animals.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "O" for oxygen atom, "S" for sulfur atom, "N" for nitrogen atom, "h" for hour or hours and "rt" for room temperature) as described in J.Org.Chem., 67-1, 24A, 2002.

Other abbreviations and definitions used are defined as follows:

Hunig's base means diisopropylethyl amine;

HATU means O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexaflourophosphate;

in vacuo means at reduced pressure;

EDCI or EDC means 1-ethyl-3-(3-dimethylaminopropyl)carbodimide;

HOBT means hydroxybenztriazole;

Fmoc means 9-fluorenylmethoxycarbonyl;

trisamine resin means tris(2-aminoethyl)amine, polymer-bound.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate,

maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

The compounds of Formula I of this invention contain a chiral center, such as at C-5 of the isoxazoline ring, and as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on substituents, additional chiral centers and other isomeric forms may be present in any of A, B, Z or R_1 group, and this invention embraces all possible stereoisomers and geometric forms in these groups.

The compounds of this invention are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound according to this invention.

The quantity of active component, that is the compound according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the

particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

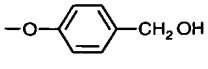
In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 1.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., 2-4 four times per day.

The compounds according to this invention may be administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound or a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound of this invention generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/mL to about 400 mg/mL of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds according to this invention are advantageously administered orally in solid and liquid dosage forms.

As a topical treatment an effective amount of Formula I is admixed in a pharmaceutically acceptable gel or cream vehicle that can be applied to the patient's skin at the area of treatment. Preparation of such creams and gels is well known in the art and can include penetration enhancers.

The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The in vitro activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically", 3rd. ed., published 1993 by the National Committee for Clinical Laboratory Standards, Villanova, Pennsylvania, USA.

Compounds in this invention can be prepared as shown in Schemes I to IV. In Scheme I an amine (**1**) is condensed with a suitably substituted carboxylic acid (HOOC-CH_2Z') to give an amide (**2**) where Z' represents Z of formula I or a group that can be transformed to Z by subsequent chemistry and where W' represents W of formula I plus NP where P is a suitable nitrogen protecting group that can be removed at an appropriate time in a manner that is compatible with other substituents on the molecule to give the primary amine (W'=NH_2) which can then be used to prepare compounds where W is NH C (X) R_1 (see the preparation of **7** in Scheme II). A variety of reagents and reaction condensations can be used for the condensations of **1** with the carboxylic acids (HOO-CH_2Z'). These include but are not limited to the carbodiimides such as dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) which can be used with promoters such as 4-(dimethylamino)pyridine (DMAP) or 1-hydroxybenzotriazole (HOBT) in solvents such as DMF or pyridine at 0°C to 50°C; and the chloroformates such as isobutyl chloroformate with a tertiary amine such as triethylamine or diisopropylethylamine in solvents such as THF at 0°C to 25°C.

Scheme II illustrates the preparation of compounds of formula I where Z is (a). In this scheme, **3** (compound **2** of Scheme I where B" is (b), Z' is  and W' is NHBoc) is allowed to react with triphenylphosphine and carbon tetrabromide in a solvent such as CH_2Cl_2 at 20°C to 40°C to give the bromide (**4**). Alkylation of primary and secondary amines with **4** can be conveniently carried out in solvents such as MeOH, EtOH and/or acetone at 0°C to 30°C. Sodium iodide can be used as a

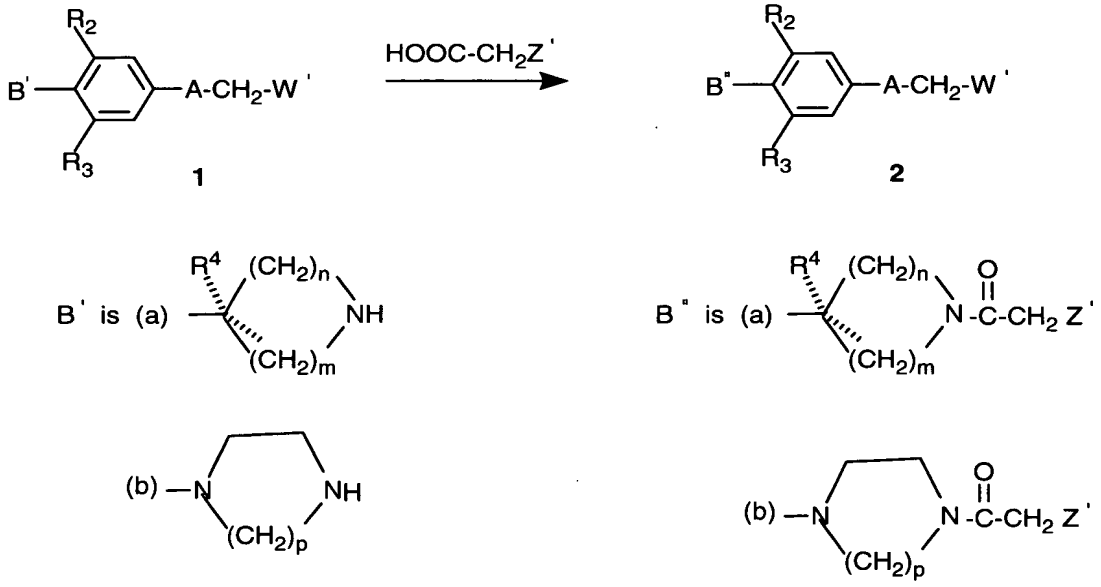
catalyst for this reaction. Removal of the *tert*-butyoxycarbonyl (Boc) protecting group of **5** (R' and R" = alkyl) to give **6** can be accomplished with an acid catalyst, conveniently 4N HCl in dioxane at 0°C to 30°C. Acylation of **6** with an activated carboxylic acid derivative such as acetic anhydride in pyridine or propionyl chloride and triethylamine in CH_2Cl_2 will give the corresponding amides (**7**, X=O). Thioacylation of **6** to give **7** (X=S) can be accomplished by the reactions of **6** with dithioesters and triethylamine in methanol; difluorothioacetamides are conveniently prepared by the reactions of **6** with an ester of difluorothioacetic acid, such as O-(3,3-diphenylpropyl) difluoroethanethioate, in a solvent such as CH_2Cl_2 and/or MeOH. A tertiary amine can be used to neutralize a salt of **6** in this reaction. Compounds of formula **7** where R' or R" is hydrogen can best be obtained by protecting the secondary amine (**5**) in this sequence with an acid stable protecting group. The 9-fluorenylmethyl carbamate (Fmoc) is suitable for this purpose. It can be removed from compound **7** by the reaction with a mild base such as piperidine. Compounds of formula **7** where both R' and R" are hydrogen can be obtained by allowing compound **4** to react with sodium azide in DMF. The resulting azide can then be reduced to the amine (**5** where R' and R" are hydrogen) by hydrogenation with a platinum or palladium catalyst. Fmoc protection of this amine, conversion to the Fmoc protected analogs of **6** and **7** and subsequent deprotection will give the desired compounds of formula **7** (R' = R" = H). Acylation of **5** (where R' and/or R" is hydrogen) with Fmoc protected amino acids or dipeptides using for example, conditions described for the preparation of **2** in Scheme I, conversion to the Fmoc protected analogs of **6** and **7** and deprotection will give **7** where R' or R" is $C(O)CH(R_7)NR_8R_9$.

Scheme III and IV illustrate the preparation of compounds of formula I where Z is (b), (c) or (d). For this type of compound it is often convenient to begin with a preformed side chain. Thus, for example, bromination of **8** with N-bromosuccinimide and light in chloroform gives **9** which is allowed to react with primary or secondary amines (HNR'R") in acetone to give **10**. At this stage secondary amines (R' or R"=H) can be acylated with activated carboxylic acid or sulfonic acid derivatives or protected with, for example, Boc, Fmoc or benzyloxycarbonyl (Cbz) groups. The ester is then hydrolyzed with an alkali metal hydroxide. It is convenient to use lithium hydroxide in mixtures of MeOH and water at ambient temperature for this reaction and the resulting salt (**11**) or the corresponding acid can be condensed with **1** as described in

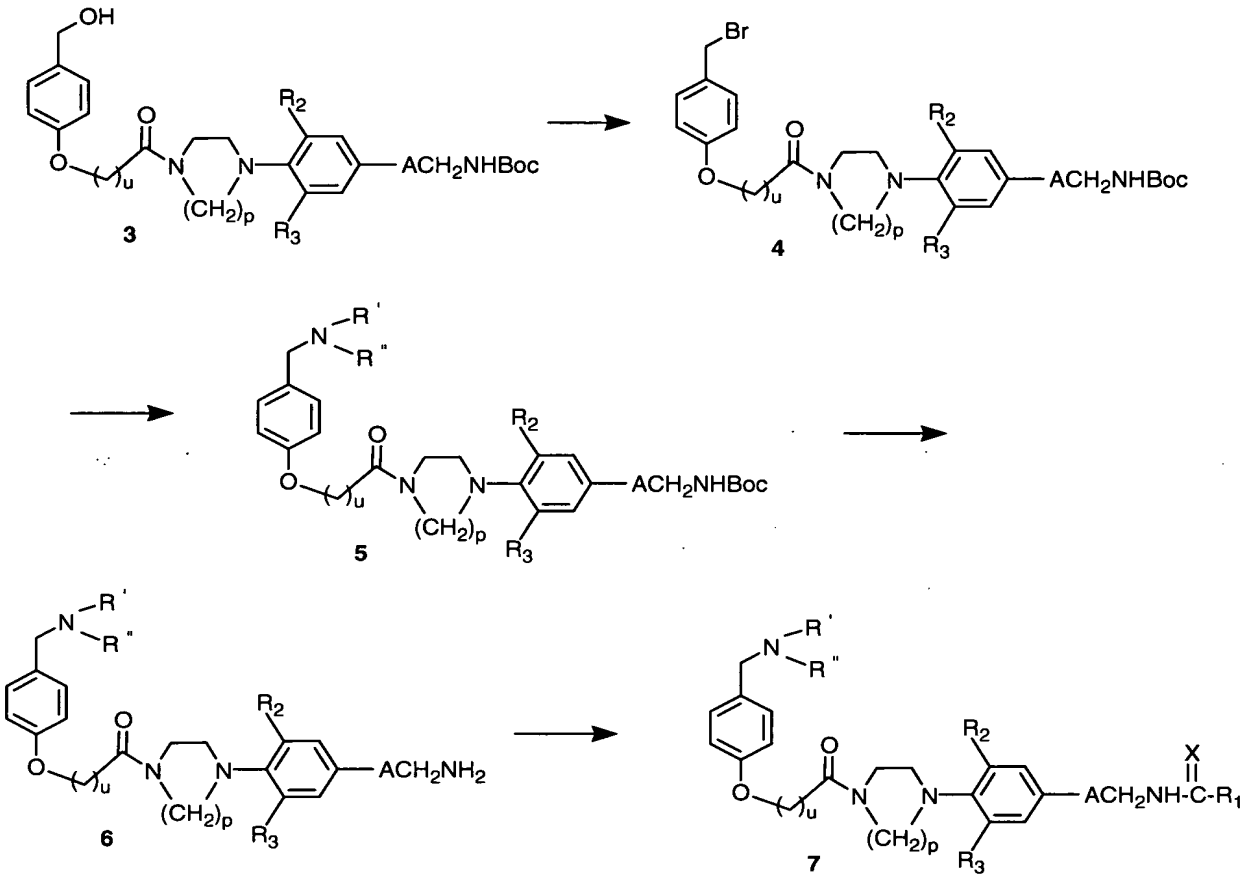
Scheme I to obtain **12**. Primary amines (**12**, R'=R"=H) are obtained by allowing **9** to react with sodium azide in DMF. Hydrolysis of the resulting azido ester to the corresponding acid and condensation with **1** gives **13**. Reduction of the azide (**13**) by hydrogenation with a palladium catalyst or other method known in the art will then give **12** (R'=R"=H) which can be converted to other desired compounds of formula I.

By using the chemistry described in Scheme III and employing other side chains known in the literature or described in the examples other compounds of formula I where Z is (b), (c), or (d) can be prepared. This is further illustrated in Scheme IV where the nitro substituted phthalimide (**14**), prepared as described in Scheme I, can be reduced by transfer hydrogenation with cyclohexene and a palladium catalyst in refluxing ethanol to give **15**. Condensation of **15** with a protected amino acid will then give **16** which can be converted to compounds of formula I as described in Schemes II and III.

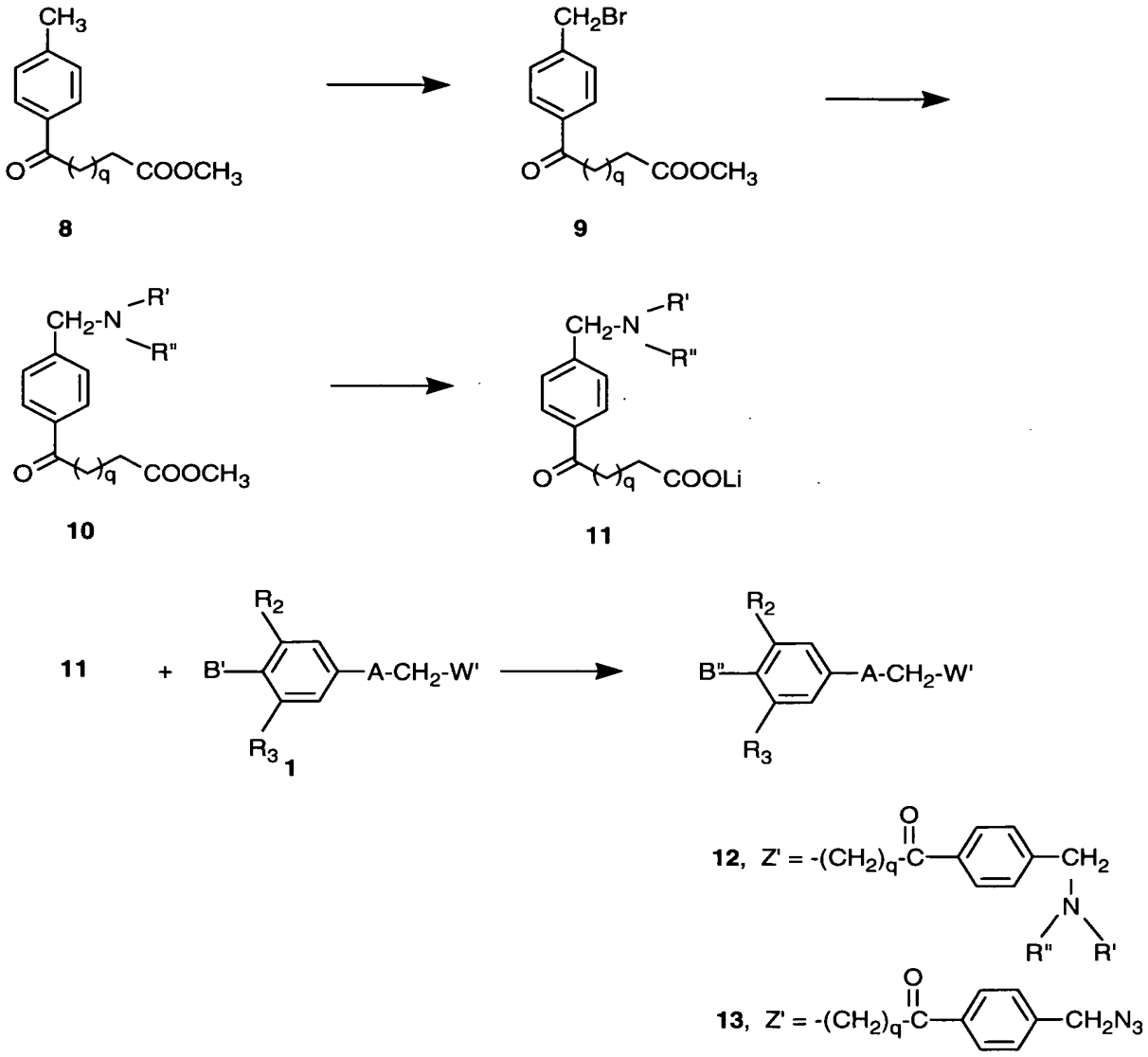
Scheme I



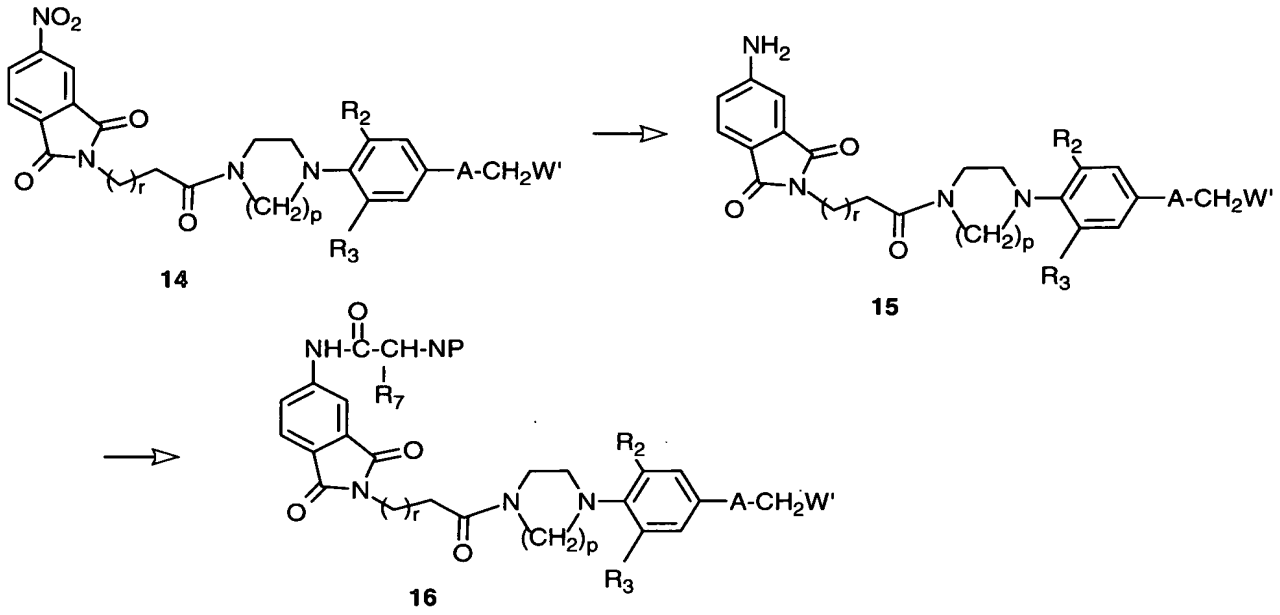
Scheme II



Scheme III


CH3
CH2Br
COOCH3
8
9
CH2-N
R'
R"
COOLi
10
11
11 + B'
A-CH2-W'
R2
R3
1
B"
12, Z' = -(CH2)q-C
13, Z' = -(CH2)q-C
CH2N3

Scheme IV



Suitable intermediates useful in preparating compounds of formula I and additional synthetic methods to assist in producing compounds of formula I may be found, for example, in the following publications each of which is hereby incorporated by reference.

U.S. Patent Nos. 5,225,565; 5,182,403; 5,164,510; 5,247,090; 5,231,188; 5,565,571; 5,547,950; 5,529,998; 5,627,181; 5,843,967; 5,861,413; 5,827,857; 5,869,659; 5,952,324; 5,968,962; 5,688,792; 6,069,160; 6,239,152; 5,792,765; 4,705,799; 5,043,443; 5,652,238; 5,827,857; 5,529,998; 5,684,023; 5,627,181; 5,698,574; 6,166,056; 6,194,441; 6,110,936; 6,069,145; 6,271,383; 5,981,528; 6,051,716; 6,043,266; 6,313,307; and 5,523,403.

U.S. Patent Application Publication 2002/0086900.

PCT Application and publications PCT/US93/04850, WO94/01110; PCT/US94/08904, WO95/07271; PCT/US95/02972, WO95/25106; PCT/US95/10992, WO96/13502; PCT/US96/05202, WO96/35691; PCT/US96/12766; PCT/US96/13726; PCT/US96/14135; PCT/US96/17120; PCT/US96/19149; PCT/US97/01970; PCT/US95/12751, WO96/15130, PCT/US96/00718, WO96/23788, WO98/54161, WO99/29688, WO99/03846, WO99/37641, WO99/37652, WO99/40094, WO97/30995, WO97/09328, WO01/81350, WO01/40236, WO00/21960 WO01/4022, and WO95/07271.

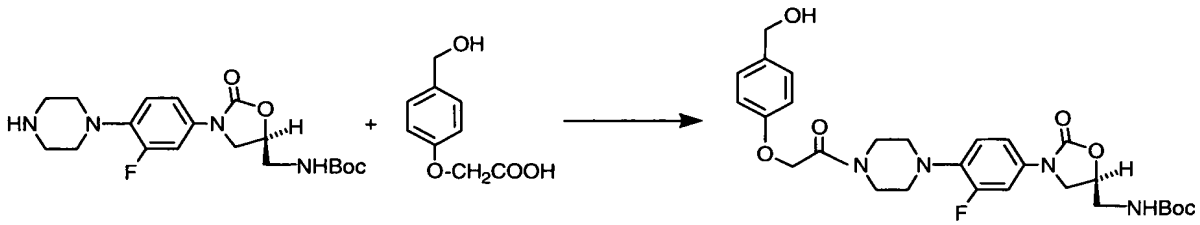
In some embodiments, the antibacterial compounds are prodrugs of the compounds of formula I. The expression "prodrug" denotes a derivative of a known direct acting drug, which is transformed into the active drug by an enzymatic or chemical process. Prodrugs of the compounds of formula I are prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include, but are not limited to, compounds of structure (I) wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to the animal, cleaves to form the free hydroxyl, amino or sulfhydryl group, respectively. Representative examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups. See Notari, R. E., "Theory and Practice of Prodrug Kinetics," Methods in Enzymology, 112:309-323 (1985); Bodor, N., "Novel Approaches in Prodrug Design," Drugs of the Future, 6(3):165-182 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in Design of Prodrugs (H. Bundgaard, ed.), Elsevier, N.Y. (1985).

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Example 1: N-[((5*S*)-3-{4-[4-({4-[(Diethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] propanethioamide (22).

Step 1:

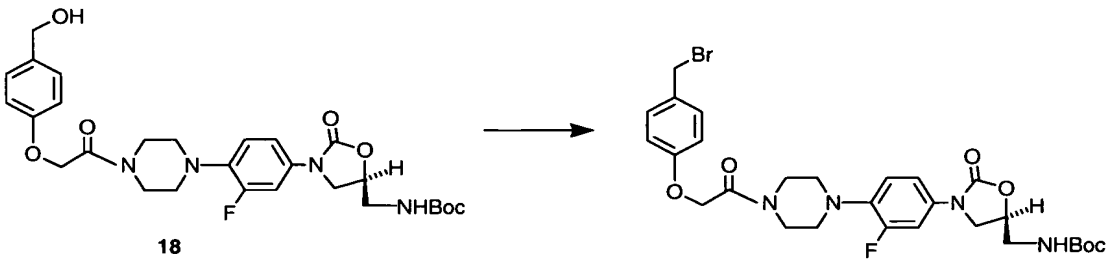


17a

18

An ice cold, stirred mixture of **17a** (15.1 g, 38.3 mmol), 4-(hydroxymethyl)phenoxyacetic acid (6.98 g, 38.3 mmol), 1-hydroxybenzotriazole hydrate (HOBT, 5.69 g, 42.1 mmol) and DMF (195 ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 14.7 g, 76.6 mmol), allowed to warm slowly to ambient temperature and stand for 18 h. It was then mixed with water (500 ml) and Et_2O (500 ml); the precipitate was collected by filtration, washed carefully with water and then 1:1 heptane: Et_2O and dried to give 19.8 g of **18**, an off-white solid. A sample of this material that had been purified by silica gel chromatography with 2.5% MeOH-CH_2Cl_2 and trituration with EtOAc-heptane had: mp 148-154°C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34 (s, 9H), 2.92, 2.98 (s, s, 4H), 3.25 (m, 2H), 3.60 (s, 4H), 3.73 (dd, 1H), 4.06 (t, 1H), 4.39 (d, 2H), 4.67 (m, 1H), 4.82 (s, 2H), 5.04 (t, 1H), 6.87 (d, 2H), 7.06 (t, 1H), 7.18 (m, 4H), 7.49 (dd, 1H);

Step 2:



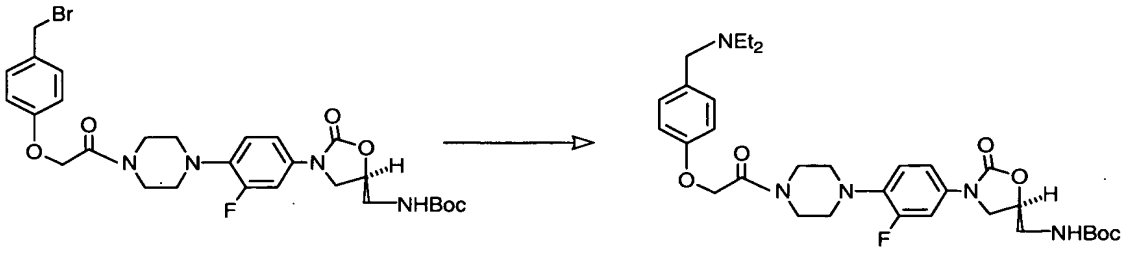
18

19

A stirred mixture of **18** (3.00 g, 5.37 mmol) and triphenylphosphine (2.16 g, 8.22 mmol) in CH_2Cl_2 (90 ml) was treated with carbon tetrabromide (2.69 g, 8.6 mmol) and kept at ambient temperature for 1 h. Additional triphenylphosphine (216 mg) and carbon tetrabromide (269 mg) were added and the mixture was stirred for 20 min and then concentrated *in vacuo*. The residue was stirred for 2 h with a mixture of Et_2O (80 ml), heptane (80 ml), and water (60 ml) and then filtered. The solid was washed with

water, 1:1 Et_2O: heptane and heptane and dried to give 3.76 g of **19** which was used without further purification: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34 (s, 9H), 2.93, 2.99 (s, s, 4H), 3.25 (m, 2H), 3.60 (s, 4H), 3.74 (dd, 1H), 4.06 (t, 1H), 4.67 (m, 1H), 4.68 (s, 2H), 4.87 (s, 2H), 6.89 (d, 2H), 7.06 (t, 1H), 7.18 (m, 2H), 7.35 (d, 2H), 7.48 (dd, 1H)

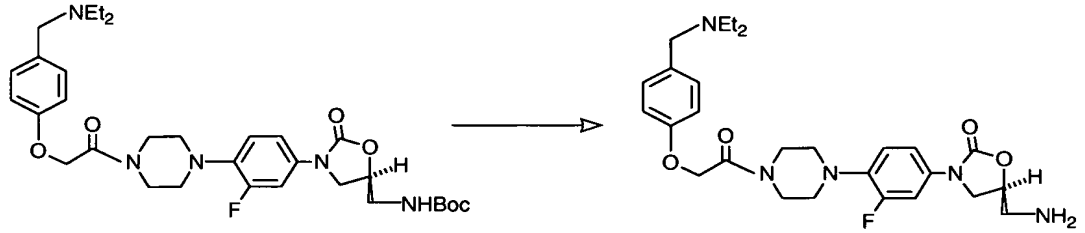
Step 3:



19 **20**

A stirred mixture of **19** (2.50 g), diethylamine (1.98 ml, 19.1 mmol), sodium iodide (15 mg) and acetone (98 ml) was kept at ambient temperature for 18 h and mixed with water (50 ml). It was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 2.44 g of **20**, a light brown foam: MS (EI) m/z 613.0 (M^+), 541.0, 485.5, 441.1, 277.1, 221.5; IR (drift) 3411, 3331, 1746, 1708, 1675 cm^{-1}.

Step 4:

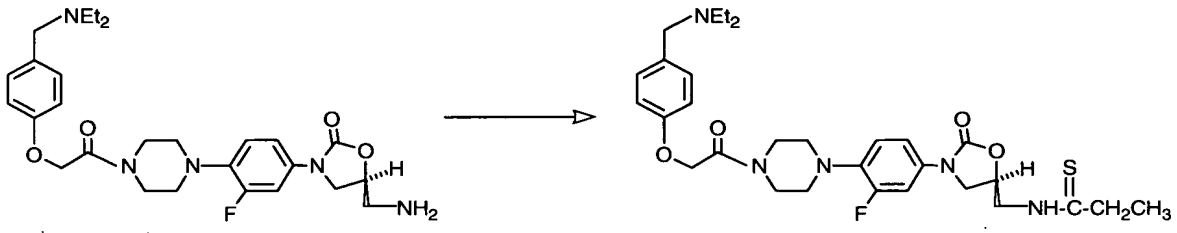


20 **21**

Compound **20** (2.44 g) was cooled in an ice bath and treated with 4N HCl in dioxane (30 ml). The mixture was stirred in the ice bath for 1 h and at ambient temperature for 1 h and then concentrated *in vacuo*. The residue was triturated three times with CH_2Cl_2 (70 ml) with concentration after each addition. A mixture of the resulting material and saturated $NaHCO_3$ (60 ml) was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 10% MeOH-1% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc-MeOH-heptane gave 1.01 g of **21**: mp 98°C with softening and foaming from 92°C;

^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 0.93 (t, 6H), 2.02 (broad s), 2.39 (q, 4H), 2.79 (m, 2H), 2.92, 2.98 (s, s, 4H), 3.42 (s, 2H), 3.60 (s, 4H), 3.80 (dd, 1H), 4.01 (t, 1H), 4.58 (m, 1H), 4.81 (s, 2H); 6.85 (d, 2H), 7.05 (t, 1H), 7.18 (m, 3H), 7.50 (dd, 1H); MS (EI) m/z 513.0 (M^+), 498.2, 484.1, 441.2, 412.1, 350.0, 335.3, 293.6.

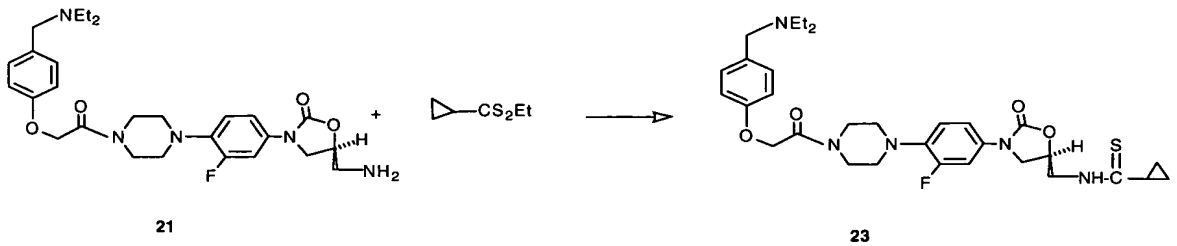
Step 5:



21 22

A stirred mixture of **21** (300 mg, 0.584 mmol), triethylamine (204 μL, 1.46 mmol) and MeOH (6.5 ml) was treated with ethyl dithiopropionate (94 mg, 0.701 mmol) and kept at ambient temperature for 18 h. It was then diluted with CH_2Cl_2, mixed with silica gel (2.5 g) and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc-heptane-Et_2O gave 155 mg of **22**, an off white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 0.94 (t, 6H), 1.22 (t, 3H), 2.39 (m, 4H), 2.56 (q, 2H), 2.92, 2.99 (s, s, 4H), 3.42 (s, 2H), 3.60 (s, 4H), 3.78 (dd, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.82 (s, 2H), 4.93 (m, 1H), 6.85 (d, 2H), 7.06 (t, 1H), 7.16 (m, 3H), 7.49 (dd, 1H), 10.32 (s, 1H).

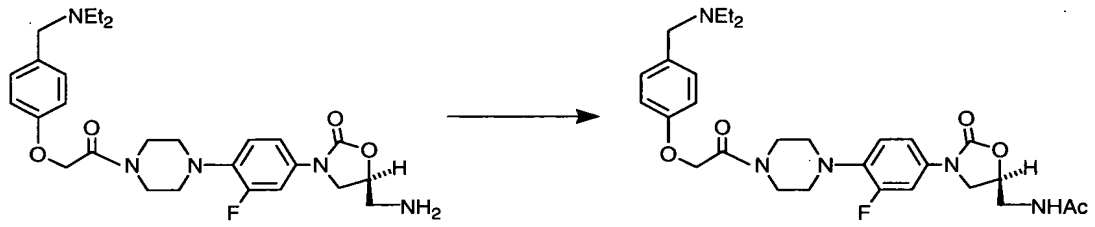
Example 2: N-[((5*S*)-3-{4-[4-({4-[(Diethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] cyclopropanecarbothioamide (23).



21 23

As described for the preparation of **22**, the reaction of **7** (300 mg, 0.584 mmol) with ethyl cyclopropanecarbodithioate gave 146 mg of **23**; ^{1}HNMR [300 MHz, $(CD_3)_2SO$] δ 0.94 (m, 10 H), 2.14 (m, 1H), 2.39 (m, 4H), 2.93, 2.99 (s, s, 4H), 3.42 (s, 2H), 3.61 (s, 4H), 3.79 (dd, 1H), 3.94 (m, 2H), 4.12 (t, 1H), 4.82 (s, 2H), 4.93 (m, 1H), 6.85 (d, 2H), 7.06 (t, 1H), 7.18 (m, 3H), 7.50 (dd, 1H), 10.52 (t, 1H); MS (EI) m/z 597.2 (M^+), 553.4, 524.4, 247.7.

Example 3: N-[((5*S*)-3-{4-[4-({4-[(Diethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (24).

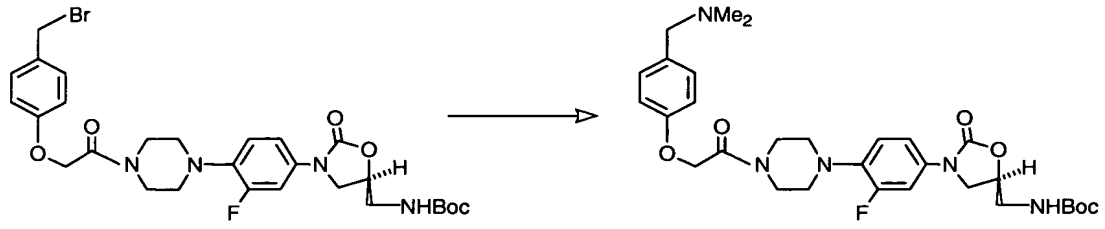


21 **24**

A stirred mixture of **21** (300 mg, 0.584 mmol), triethylamine (0.65 ml, 4.7 mmol), THF (5.8 ml) and CH_2Cl_2 (5.8 ml) was treated with acetyl chloride (76 μL, 0.88 mmol) and kept at ambient temperature for 18 h. It was then diluted with CH_2Cl_2, mixed with silica gel (2.5 g) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc-heptane-Et_2O gave 122 mg of **24**, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.17 (m, 6H), 1.81 (s, 3H), 3.02 (m, 8H), 3.38 (t, 2H), 3.60 (s, 4H), 3.70 (dd, 1H), 4.07 (t, 1H), 4.19 (d, 2H), 4.79 (m, 1H), 4.91 (s, 2H), 6.98 (d, 2H), 7.06 (t, 1H), 7.16 (dd, 1H), 7.48 (m, 3H), 8.26 (t, 1H).

Example 4: N-[((5*S*)-3{4-[4-({4-[(Dimethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] propanethioamide (27).

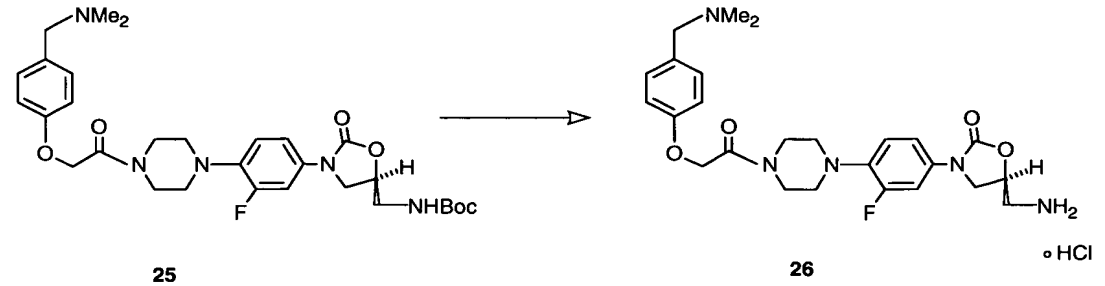
Step 1:



19 25

A stirred mixture of **19** (1.88 g), 2M dimethylamine in MeOH (5.1 ml, 10.2 mmol), sodium iodide (36 mg) and acetone (66 ml) was kept at ambient temperature for 20 min and concentrated *in vacuo*. A mixture of the residue and 1N HCl was washed with Et_2O and EtOAc, cooled in an ice bath and made alkaline with solid $NaHCO_3$. This was extracted with CH_2Cl_2 and the extract was concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 gave 979 mg of **25** that was used without further purification in subsequent reactions: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.33 (s, 9H), 2.14 (s, 6H), 2.92, 2.98 (s, s, 4H), 3.24 (t, 2H), 3.36 (s, 2H), 3.60 (s, 4H), 3.74 (dd, 1H), 4.06 (t, 1H), 4.66 (m, 1H), 4.83 (s, 2H), 6.87 (d, 2H), 7.05 (t, 1H), 7.16 (m, 4H), 7.48 (dd, 1H); MS (EZ) m/z 585.1 (M^+), 541.3, 528.2, 512.2, 485.2, 470.2, 277.2, 262.5.

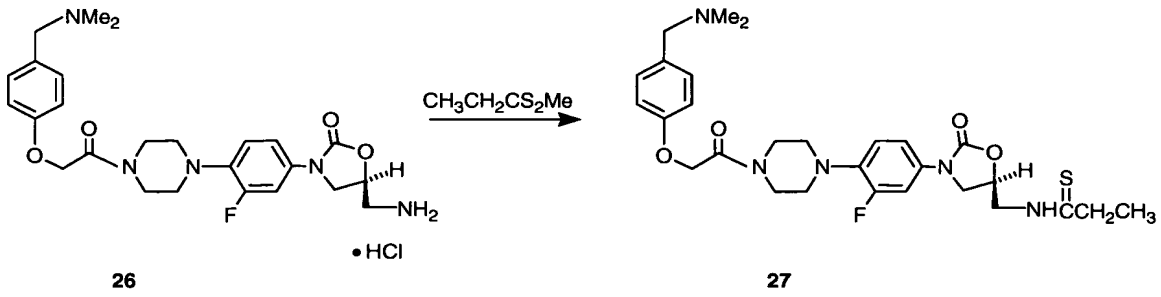
Step 2:



25 26

Solid **25** (357 mg) was cooled in an ice bath and treated with 4N HCl in dioxane (10 ml). The stirred mixture was kept in the ice bath for 1 h and at ambient temperature for 1 h and then concentrated *in vacuo*. The residue was triturated three times with 50 ml portions of CH_2Cl_2, concentrating the mixture after each addition, to give **26**, a white solid: MS (EI) m/z 485.2 (M^+), 470.3, 442.4, 335.7, 293.6, 261.6; IR(drift) 3330, 1757, 1662, 1627 cm^{-1}.

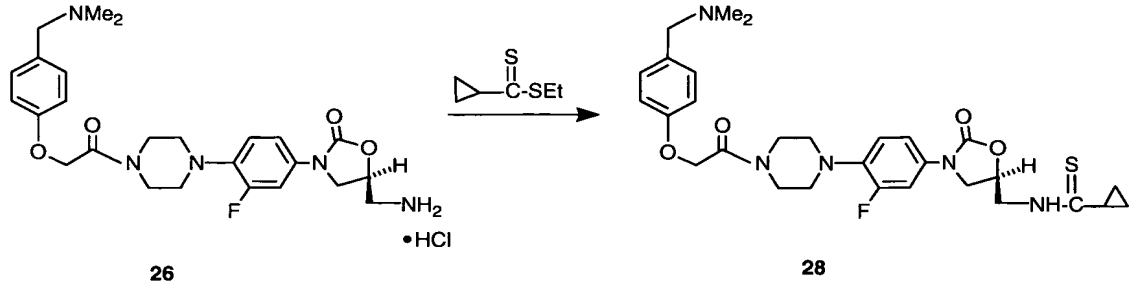
Step 3:



26 27

A stirred mixture of **26** (prepared from 357 mg of **25**), triethylamine (0.68 ml, 4.88 mmol) and MeOH (8.5 ml) was treated with methyl dithiopropionate[4] (293 mg, 2.44 mmol), and kept at ambient temperature for 3 h. It was then concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc gave 204 mg of **13** a white solid: mp 163-164°C; ^{1}HNMR [300 MHz, $(CD_3)_2SO$] δ 1.12 (t, 3H), 2.09 (s, 6H), 2.56 (q, 2H), 2.92, 2.99 (s, s, 4H), 3.28 (s, 2H), 3.60 (s, 4H), 3.78 (dd, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.82 (s, 2H), 4.93 (m, 1H), 6.86 (d, 2H), 7.06 (t, 1H), 7.15 (m, 3H), 7.49 (dd, 1H), 10.30 (t, 1H); MS (EI) m/z 557.1 (M^+), 513.1, 354.1, 165.4; MS (CI) m/z 558.1 ($M+H^+$); IR (drift) 3235, 1750, 1653 cm^{-1}. Anal. calcd for $C_{28}H_{36}FN_5O_4S$: C, 60.30; H, 6.51; N, 12.56. Found: C, 60.08; H, 6.47; N, 12.44 cm^{-1}

Example 5: N-[((5*S*)-3-{4-[4-({4-[(Dimethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] cyclopropanecarbothioamide (28).

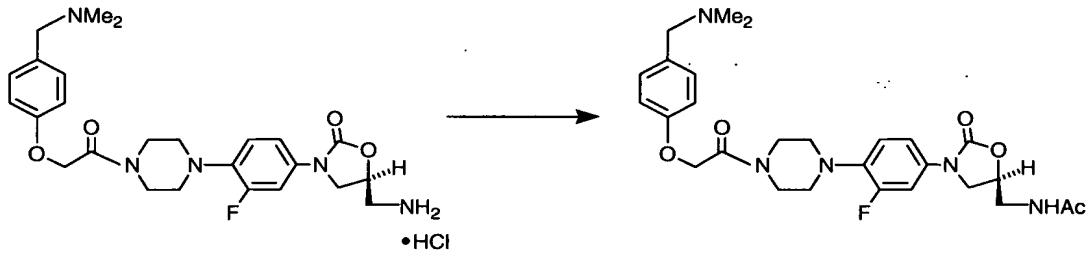


26 28

As described for the preparation of **27**, the reaction of **26** (prepared from 357 mg of **25**) with ethyl cyclopropanecarbodithioate and triethylamine gave the thioamide which was mixed with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel

with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from Et_2O-CH_2Cl_2-heptane gave 74 mg of **28**: mp 169-170°C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 0.84 (m, 2H), 1.01 (m, 2H), 2.12 (s, 7H), 2.93. 3.00 (s, s, 4H), 3.25 (s, 2H), 3.60 (s, 4H), 3.79 (dd, 1H), 3.94 (m, 2H), 4.12 (t, 1H), 4.83 (s, 2H), 4.92 (m, 1H), 6.86 (d, 2H), 7.07 (t, 1H), 7.17 (m, 3H), 7.49 (dd, 1H).

Example 6: N-[((5*S*)-3-{4-[4-({4-[(Dimethylamino)methyl]phenoxy}acetyl) piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (29).

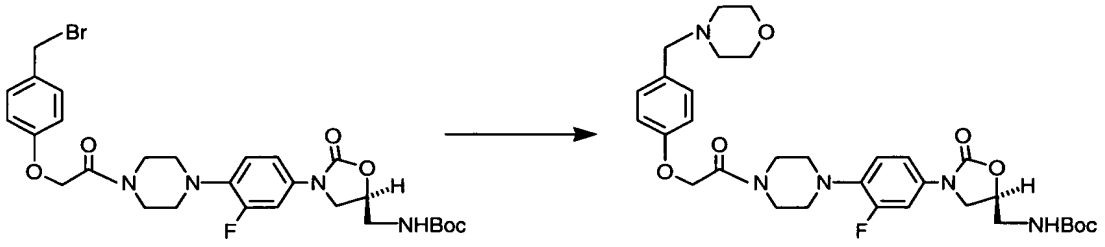


26 29

As described for the preparation of **27**, the reaction of **26** (prepared from 264 mg of **25**) with acetyl chloride and triethylamine gave the acetamide which was purified by silica gel chromatography with 5% MeOH-0.5%NH_4OH-CH_2Cl_2 followed by crystallization from Et_2OAc to give 73 mg of **29**, a white solid; ^{1}HNMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.45 (s, 6H), 2.93. 3.00 (s, s, 4H), 3.38 (t, 2H), 3.60 (s, 4H), 3.68 (dd, 1H), 3.85 (s, 2H), 4.06 (t, 1H), 4.69 (m, 1H), 4.88 (s, 2H), 6.94 (d, 2H), 7.06 (t, 1H), 7.16 (dd, 1H), 7.33 (d, 2H), 7.49 (dd, 1H), 8.24 (t, 1H).

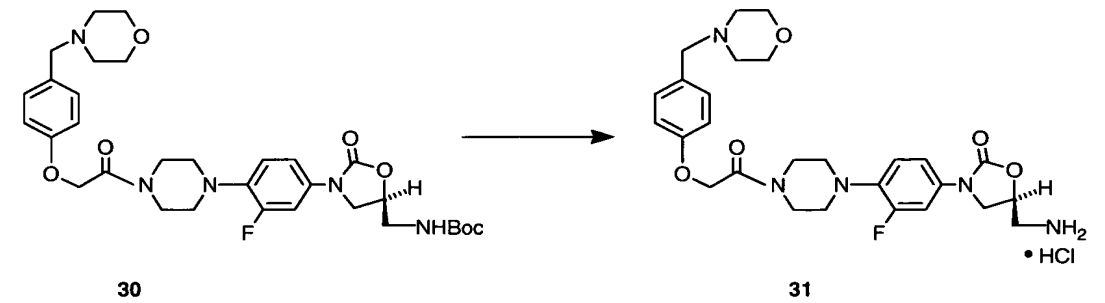
Example 7: N-({(5*S*)-3-[3-Fluoro-4-(4-{[4-(morpholin-4-ylmethyl)phenoxy] acetyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) propanethioamide (32).

Step 1:



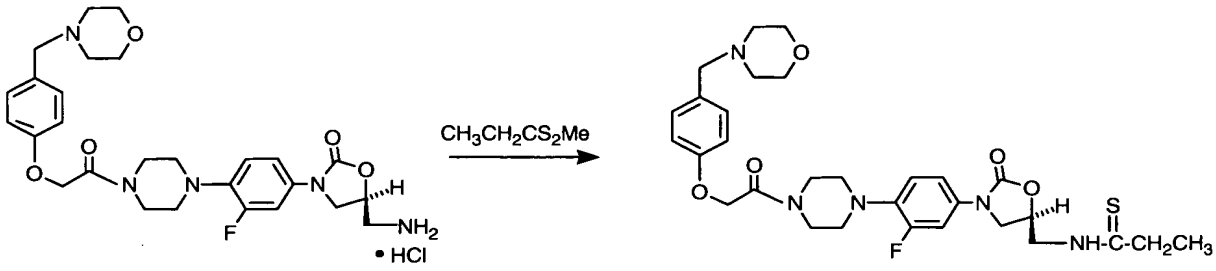
A stirred mixture of **19** (1.88 g), morpholine (1.1 ml, 12.8 mmol) sodium iodide (36 mg) and acetone (29 ml) was kept at ambient temperature for 18 h and concentrated *in vacuo*. A mixture of the residue in 1N HCl (15 ml) was washed with Et_2O and EtOAc, cooled in an ice bath and made alkaline with solid $NaHCO_3$. It was extracted with CH_2Cl_2 and the extract was concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 gave 773 mg of **30**. Rechromatography of the impure fractions with 2.5% MeOH-0.25% NH_4OH-CH_2Cl_2 and trituration of the product with EtOAc-heptane gave 280 mg of additional **15**: mp 166-168°C; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.33 (s, 9H), 2.29 (s, 4H), 2.92, 2.98 (s, s, 4H), 3.24 (t, 2H), 3.35 (s, 2H), 3.53 (t, 4H), 3.60 (s, 4H), 3.74 (dd, 1H), 4.06 (t, 1H), 4.66 (m, 1H), 4.82 (s, 2H), 6.86 (d, 2H), 7.05 (t, 1H), 7.19 (m, 4H), 7.48 (dd, 1H).

Step 2:



As described for the preparation of **26** the reaction of **30** (770 mg, 1.23 mmol) with 4N HCl in dioxane gave **31**: MS (EI) m/z 527.2 (M^+), 441.5, 334.4; IR (drift) 3330, 1758, 1666, 1626 cm^{-1}.

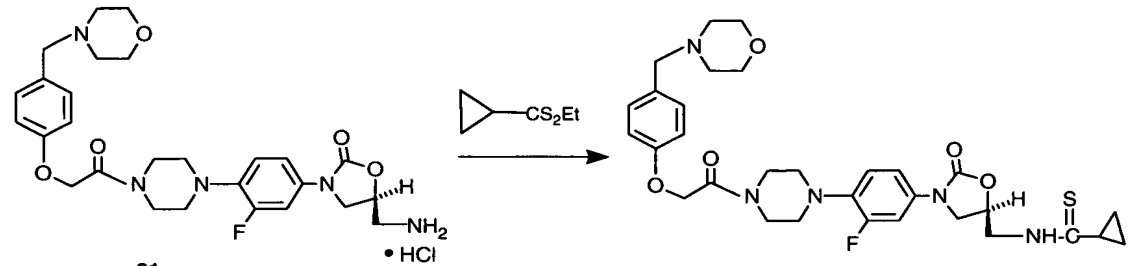
Step 3:



31 32

As described for the preparation of **27**, the reaction of **31** (prepared from 385 mg of **30**) with methyl dithiopropionate and crystallization of the product from EtOAc-heptane gave 308 mg of **32**: mp 159-160°C; ^{1}HNMR [300 MHz, $(CD_3)_2SO$] δ 1.12 (t, 3H), 2.29 (s, 4H), 2.56 (q, 2H), 2.92, 2.99 (s, s, 4H), 3.35 (s, 2H), 3.53 (t, 4H), 3.60 (s, 4H), 3.78 (dd, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.82 (s, 2H), 4.93 (m, 1H), 6.86 (d, 2H), 7.06 (t, 1H), 7.17 (m, 3H), 7.49 (dd, 1H), 10.30 (t, 1H); MS (FAB) m/z 600 ($M+H^+$), 599.4, 513.3; HRMS calcd for $C_{30}H_{39}FN_5O_5S$ ($M+H^+$), 600.2656, found 600.2666; IR (drift) 3306, 3236, 1749, 1653 cm^{-1}. Anal. calcd for $C_{30}H_{38}FN_5O_5S$: C, 60.08; H, 6.39; N, 11.68. Found: C, 59.60; H, 6.47; N, 11.56.

Example 8: N-({(5*S*)-3-[3-Fluoro-4-(4-{[4-(morpholin-4-ylmethyl)phenoxy] acetyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl) cyclopropanecarbothioamide (33).

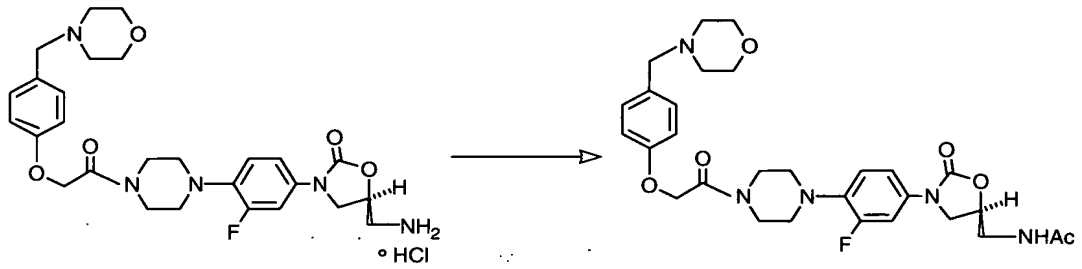


31 33

As described for the preparation of **27**, the reaction of **31** (prepared from 385 mg of **25**) with ethyl cyclopropanecarbodithioate and crystallization of the product from EtOAc-heptane gave 290 mg of **33**: mp 138-141°C; ^{1}H NMR[300 MHz, $(CD_3)_2SO$] δ 0.84 (m, 2H), 1.01 (m, 2H), 2.14 (m, 1H), 2.29 (s, 4H), 2.93, 2.99 (s, s, 4H), 3.35 (s,

2H), 3.53 (t, 4H), 3.60 (s, 4H), 3.78 (dd, 1H), 3.94 (m, 2H), 4.12 (t, 1H), 4.82 (s, 2H), 4.93 (m, 1H), 6.86 (d, 2H), 7.06 (t, 1H), 7.17 (m, 3H), 7.50 (dd, 1H), 10.50 (t, 1H);

Example 9: N-({(5*S*)-3-[3-Fluoro-4-(4-{[4-(morpholin-4-ylmethyl)phenoxy] acetyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (34).

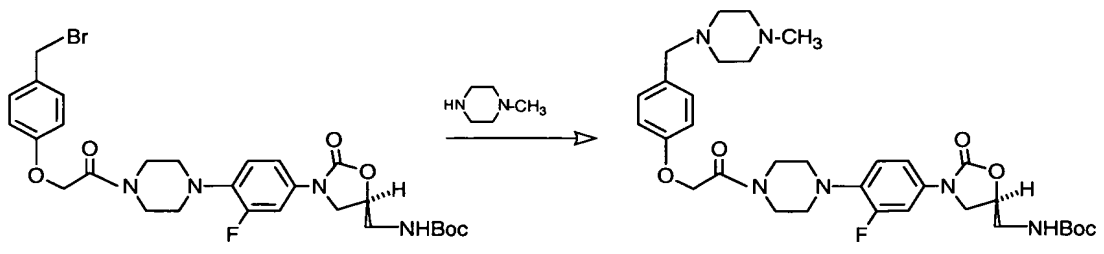


31 34

As described for the preparation of **24**, the reaction of **31** (prepared from 260 mg of **30**) with acetyl chloride and triethylamine and crystallization of the product from EtOAc-heptane gave 194 mg of **34**, a white solid; mp 143-147°C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.29 (s, 4H), 2.92, 2.99 (s, s, 4H), 3.36 (s, 2H), 3.38 (t, 2H), 3.53 (s, 4H), 3.60 (s, 4H), 3.68 (dd, 1H), 4.06 (t, 1H), 4.69 (m, 1H), 4.82 (s, 2H), 6.86 (d, 2H), 7.05 (t, 1H), 7.17 (m, 3H), 7.48 (dd, 1H), 8.23 (t, 1H).

Example 10: N-[((5*S*)-3-{3-Fluoro-4-[4-({4-[(4-methylpiperazin-1-yl)methyl] phenoxy}acetyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] propanethioamide (37).

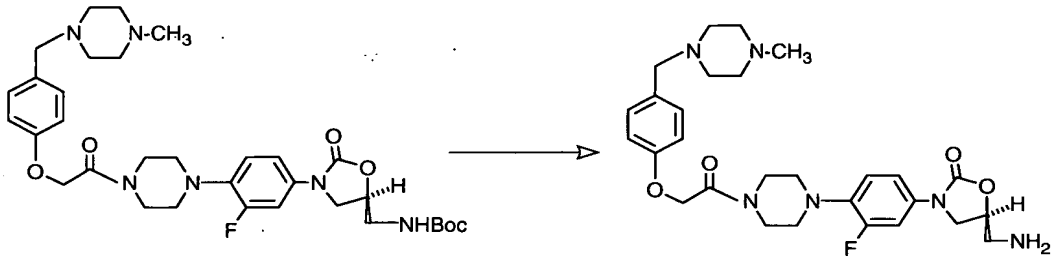
Step 1:



19 35

A stirred mixture of **19** (2.50 g), N-methyl-piperazine (2.10 ml, 19.1 mmol), acetone (98 ml) and a small amount of NaI was kept at ambient temperature for 18 h and concentrated *in vacuo*. A solution of the residue in 1N HCl (20 ml) was washed with EtOAc and then Et_2O (emulsions which were difficult to separate were formed in this process). The aqueous layer was adjusted to pH 10 with solid $NaHCO_3$ and extracted with CH_2Cl_2. The extract was concentrated to give 1.67 g of **35**, a brown foam: MS (EI) m/z 640.1 (M^+), 611.0, 582.0, 540.0, 394.1, 262.5; HRMS calcd for $C_{33}H_{46}FN_6O_6$ ($M+H^+$) 641.3463, found 641.3455.

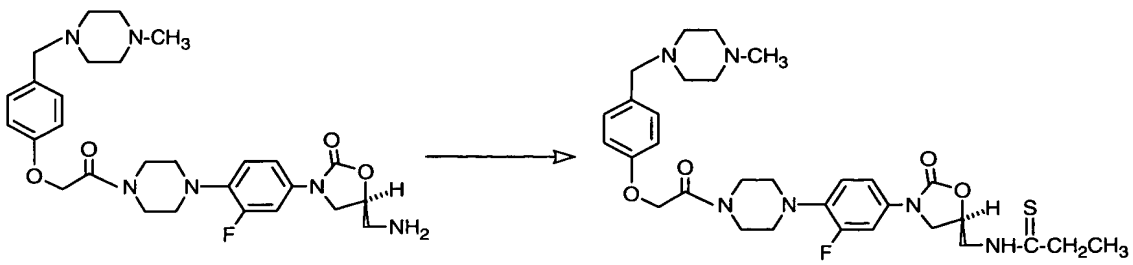
Step 2:



35 **36**

Compound **35** (1.67 g) was cooled in an ice bath and treated with 4N HCl in dioxane (20 ml). The stirred mixture was kept in the ice bath for 1 h and at ambient temperature for 1 h and concentrated *in vacuo*. The residue was triturated with three portions of CH_2Cl_2 (50 ml) with concentration after each addition. A mixture of the solid residue and saturated $NaHCO_3$ (50 ml) was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 10% MeOH-1% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc-CH_2Cl_2-heptane gave 389 mg, mp 134-135°C which contained a small amount of less polar impurity by TLC, and 567 mg, mp 138-141°C of pure **36**: MS (EI) m/z 540.0 (M^+), 511.0, 469.1, 454.3, 441.1, 350.1; IR (drift) 3325, 3313, 1730, 1664 cm^{-1}.

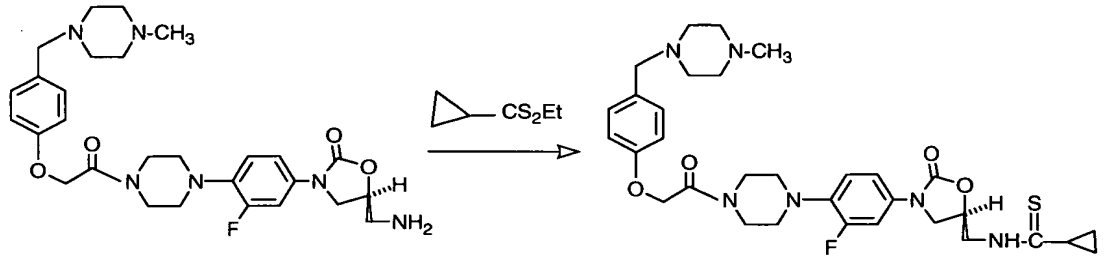
Step 3:



36 **37**

A stirred mixture of **36** (300 mg, 0.555 mmol), triethylamine (193 µL, 1.39 mmol), ethyl dithiopropionate (89 mg, 0.67 mmol) and MeOH (6 ml) was kept at ambient temperature for 18 h, treated with silica gel (2.5 g) and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from Et_2O-CH_2Cl_2 gave 175 mg of **37**, a white solid: mp 139-144°C (dec); ^1H NMR [300 MHz, (CD_3SO] δ 1.15 (t, 3H), 2.18 (s, 3H), 2.35 (broad s, 8H), 2.58 (q, 2H), 2.95, 3.00 (s, s, 4H), 3.38 (s, 2H), 3.62 (s, 4H), 3.81 (dd, 1H), 3.92 (t, 2H), 4.13 (t, 1H), 4.84 (s, 2H), 4.95 (m, 1H), 6.88 (d, 2H), 7.08 (t, 1H), 7.18 (m, 3H), 7.51 (dd, 1H), 10.35 (s, 1H).

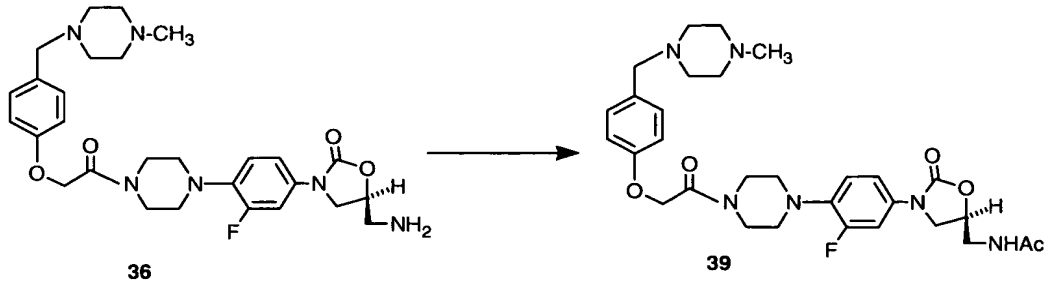
Example 11: N-[((5*S*)-3-{3-Fluoro-4-[4-({4-[(4-methylpiperazin-1-yl)methyl]phenoxy}acetyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide (38).



36 **38**

Compound **38** was prepared by the reaction of **36** (250 mg, 0.462 mmol) with ethyl cyclopropanecarbodithioate as described for the preparation of **37**. Crystallization of the product from Et_2O-CH_2Cl_2 gave a solid which was mixed with saturated $NaHCO_3$, extracted with CH_2Cl_2: MeOH (9:1) and crystallized: IR (drift) 3302, 1739, 1638 cm-1; MS (CI) m/z 625.2 ($M+H^+$), 581.2; HRMS (FAB) calcd for $C_{32}H_{42}FN_6O_4S$ ($M+H^+$) 625.2972, found 625.2961.

Example 12: N-[((5*S*)-3-{3-Fluoro-4-[4-({4-[(4-methylpiperazin-1-yl)methyl] phenoxy}acetyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl] acetamide (39).

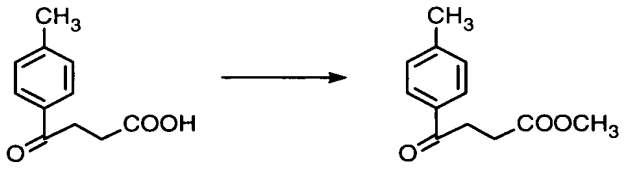


36 39

A stirred solution of **36** (250 mg, 0.462 mmol), triethylamine (515 µL, 3.70 mmol), CH_2Cl_2 (4.6 ml) and THF (4.6 mmol) was treated with acetyl chloride (60 µL, 0.69 mmol), kept at ambient temperature for 18 h, treated with silica gel (2.5 g) and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 gave the product which was crystallized from Et_2O-CH_2Cl_2. The resulting material appeared to be a salt. It was mixed with saturated $NaHCO_3$ and extracted with 9:1 CH_2Cl_2: MeOH. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from EtOAc gave **39**: IR (drift) 3317, 1726, 1668, 1645 cm^{-1}; MS (EI) m/z 582.3 (M^+), 538.3, 524.2, 511.2, 467.2, 439.2, 336.2, 294.1; HRMS (FAB) calcd for $C_{30}H_{40}FN_6O_5$ ($M+H^+$) 583.3044, found 583.3045.

EXAMPLE 13: N-[((5*S*)-3-{4-[4-(4-{4-[(Dimethylamino)methyl]phenyl}-4-oxobutanoyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (47).

Step 1:

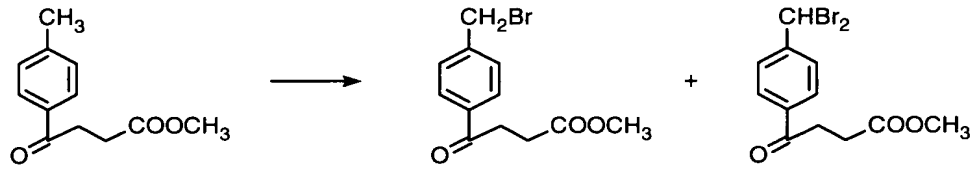


40

A stirred mixture of 4-(4-methylphenyl)-4-oxobutanoic acid (5.00 g, 26.0 mmol) and potassium carbonate (10.8 g, 78.0 mmol) in DMF (50 ml) was treated with methyl iodide (8.1 ml, 130 mmol) and kept at ambient temperature for 3 h. It was then mixed with water (300 ml) and extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$) and concentrated to give 5.09 g of a light yellow solid (**40**): mp 40-42°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.75 (t, 2H), 3.30 (t, 2H), 3.70 (s,

3H), 7.26 (d, 2H), 7.88 (d, 2H); MS (ESI) m/z 229 ($M+Na^+$); IR (drift) 1733, 1679 cm^{-1}.

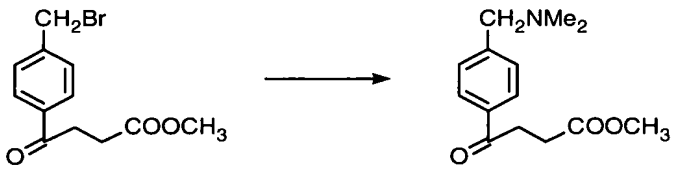
Step 2:



40 **41** **42**

A stirred mixture of **40** (22.0 g, 107 mmol), N-bromosuccinimide (23.7 g, 133 mmol) and $CHCl_3$ (1600 ml) was kept under a bright (movie) light for 2 h; the mixture refluxed gently. Additional NBS (2.3 g) was added and stirring under the light was continued for 2 h. This mixture was concentrated *in vacuo* and the residue was stirred for three days with Et_2O (1 L) and then filtered. The solid was washed well with Et_2O and the filtrate was washed with water, dried ($MgSO_4$) and concentrated. The residue was triturated with 1:1 Et_2O-heptane at ambient temperature for 30 min and at 0°C for 30 min and then filtered to give 22.5 g of an off-white solid that by NMR was an 85:15 mixture of **41** and **42**: ^1H NMR (300 MHz, $CDCl_3$ for **4**) δ 2.77 (t, 2H), 3.31 (t, 2H), 3.71 (s, 3H), 4.50 (s, 2H), 7.49 (d, 2H), 7.96 (d, 2H); ^1H NMR (300 MHz, $CDCl_3$ for **5**) δ 2.78 (t, 2H), 3.31 (t, 2H), 3.71 (s, 3H), 6.65 (s, 1H), 7.66 (d, 2H), 7.98 (d, 2H). A sample of this mixture was purified by silica gel chromatography with 25% EtOAc-heptane to give a sample of **41** with 99.6% purity: mp 163-164°C; IR (drift) 1729, 1680 cm^{-1}; MS (ESI) m/z 284, 286 (M^+); HRMS calcd for $C_{12}H_{14}BrO_3$ ($M+H^+$) 285.0127, found 285.0132.

Step 3:

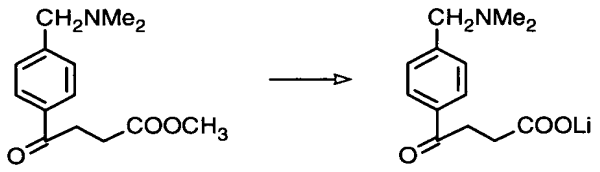


41 **43**

A stirred mixture of an 86:14 mixture of **41** and **42** (200 mg), 2 M dimethylamine in MeOH (1.4 ml) and sodium iodide (7 mg) in acetone (9 ml) was kept at ambient temperature for 18 h and concentrated *in vacuo*. A solution of the residue in 1N

hydrochloric acid (5 ml) was washed with Et_2O, made alkaline with 2N NaOH and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated to give 124 mg of **43** which was purified by silica gel chromatography with 5% MeOH-CH_2Cl_2: ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 6H), 2.76 (t, 2H), 3.32 (t, 2H), 3.47 (s, 2H), 3.70 (s, 3H), 7.41 (d, 2H), 7.94 (d, 2H).

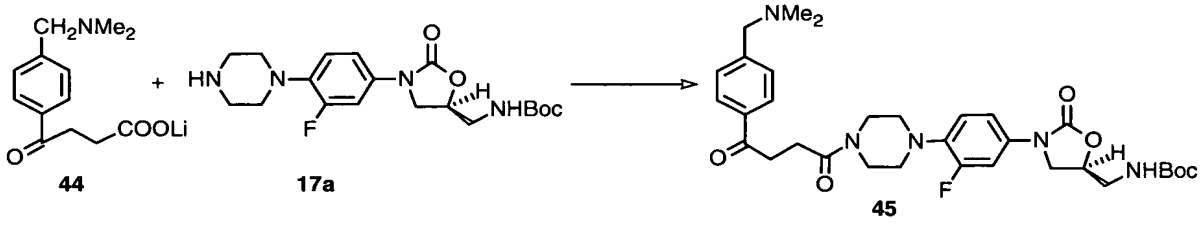
Step 4:



43 **44**

A stirred solution of **43** (632 mg, 2.53 mmol) in MeOH (17 ml) was treated with 1 M LiOH (3.3 ml) and kept at ambient temperature for 5 h. Additional LiOH (1.0 ml) was added and the mixture was kept at ambient temperature for 18 h and concentrated *in vacuo*. The residue was triturated with Et_2O, filtered, washed with Et_2O and dried to give 732 mg of **44**, an off-white solid: mp 198-199°C; MS (EI) m/z 234.8 (M-Li+H^+); MS (CI) m/z 236.3 (M-Li+2H^+), IR (drift) 1679 cm^{-1}.

Step 5:



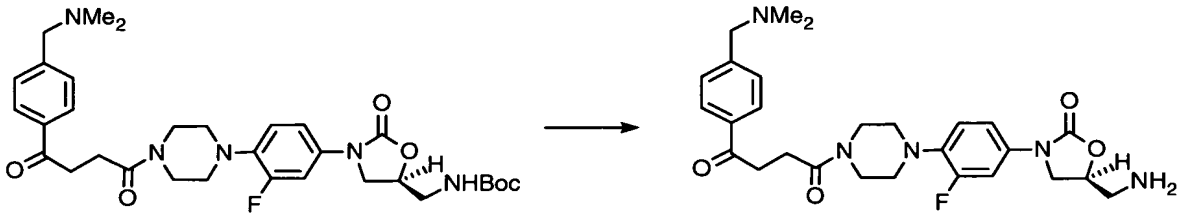
44 **17a** **45**

A stirred, ice cold mixture of **44** (2.5 mmol), **17a** (986 mg, 2.50 mmol), triethylamine (1.05 ml, 7.50 mmol) and hydroxybenzotriazole hydrate (HOBT) (372 mg, 2.75 mmol)

in DMF (22 ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.05 g, 5.50 mmol), warmed to ambient temperature and kept for 18 h. It was then mixed with water (100 ml) and Et_2O (75 ml). A solid precipitated. The Et_2O layer and solid was washed with water; the solid was collected by filtration, washed with Et_2O and dried to give 1.25 g of **45**: mp 160-164°C; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34 (s, 9H), 2.14 (s, 6H), 2.73 (t, 2H), 2.90, 3.01 (s, s,

4H), 3.22 (m, 4H), 3.44 (s, 2H), 3.58, 3.65 (s, s, 4H), 3.74 (dd, 1H), 4.07 (t, 1H), 4.66 (m, 1H), 7.08 (t, 1H), 7.19 (m, 2H), 7.42 (d, 2H), 7.49 (dd, 1H), 7.93 (d, 2H).

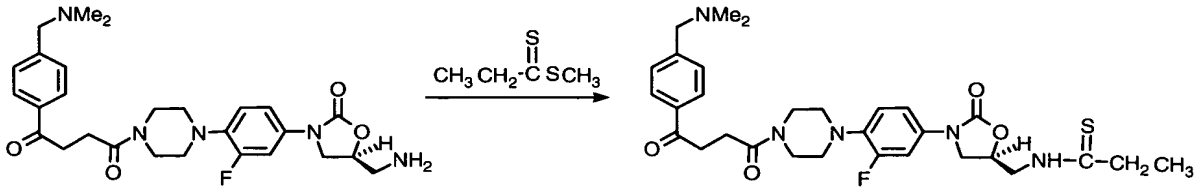
Step 6:



45 46

A flask containing **45** (1.20 g, 1.96 mmol) was cooled in an ice bath and treated with 4N hydrogen chloride in dioxane (10 ml). The mixture was stirred in the ice bath for 2 h and at ambient temperature for 1.5 h and then concentrated *in vacuo*. The residue was triturated with three 40 ml portions of CH_2Cl_2 with concentration after each addition to give **46**, a white solid: mp > 210°C; MS (EI) m/z 511.2 (M^+); IR (drift) 3352, 1759, 1685, 1645, 1629 cm^{-1}.

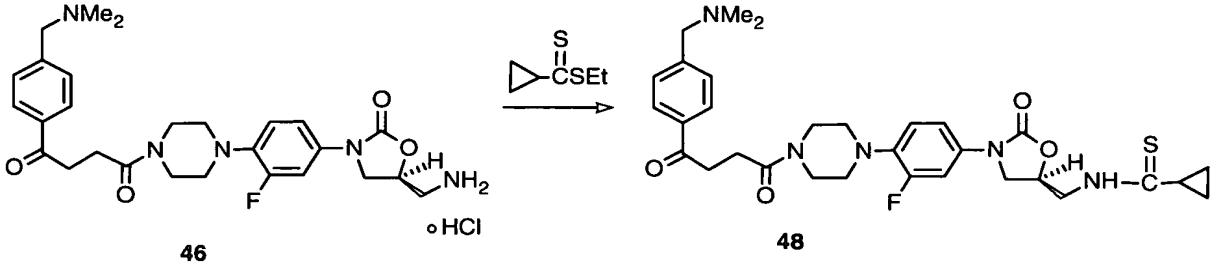
Step 7:



46 47

A stirred mixture of **46** (0.98 mmol), triethylamine (1.1 ml, 7.84 mmol), methyl dithiopropionate (471 mg, 3.92 mmol) and MeOH (13.6 ml) was kept at ambient temperature for 3 d and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc gave 360 mg of **47**, a white solid: mp 169°C; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.13 (t, 3H), 2.14 (s, 6H), 2.57 (q, 2H), 2.73 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.22 (t, 2H), 3.45 (s, 2H), 3.58, 3.66 (s, s, 4H), 3.80 (d, d, 1H), 3.90 (t, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.16 (dd, 1H), 7.42 (d, 2H), 7.48 (dd, 1H), 7.93 (d, 2H), 10.30 (t, 1H);

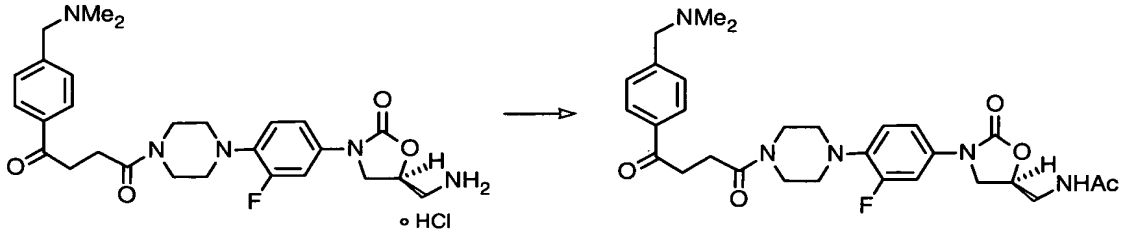
Example 14: N-[((5*S*)-3-{4-[4-(4-{4-[(Dimethylamino)methyl]phenyl}-4-oxobutanoyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide (48).



46 48

A stirred mixture of **46** (0.98 mmol), triethylamine (1.1 ml, 7.8 mmol) and MeOH (13.6 ml) was treated with ethyl cyclopropanecarbodithioate (573 mg, 3.92 mmol), kept at ambient temperature for 3 days and concentrated. The residue was chromatographed on silica gel and the product was crystallized from EtOAc to give 375 mg of **48**, a white solid: mp 174-175°C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 0.84 (m, 2H), 1.02 (m, 2H), 2.14 (s, 6H), 2.14 (m, 1H), 2.73 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.22 (t, 2H), 3.45 (s, 2H), 3.58, 3.66 (s, s, 4H), 3.79 (dd, 1H), 3.94 (m, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.18 (dd, 1H), 7.43 (d, 2H), 7.50 (dd, 1H), 7.93 (d, 2H), 10.47 (s, 1H); MS (CI) m/z 596 ($M+H^+$), 551.2, 536.1, 509.1, 218.1, 174.8, 161.2, 58.1.

Example 15: N-[((5*S*)-3-{4-[4-(4-{4-[(Dimethylamino)methyl]phenyl}-4-oxobutanoyl)-1-piperazinyl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (49).



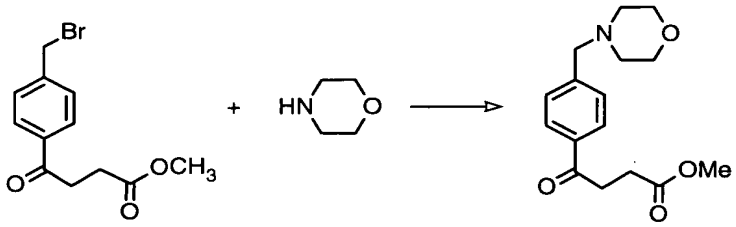
46 49

A stirred mixture of **46** (0.981 mmol), CH_2Cl_2 (10 ml), THF (10 ml) and triethylamine (1.1 ml, 7.85 mmol) was treated with acetyl chloride (128 µL, 1.47

mmol), kept at ambient temperature for 3 days and concentrated *in vacuo*. The residue was mixed with water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc gave 369 mg of **49**, and off-white solid: mp 190-192°C; MS (EI) m/z 553.2 (M^+), 509.2, 467.4, 334.3, 218.2, 134.1, 84.1, 58.5; IR (drift) 3315, 1743, 1686, 1647 cm^{-1}. Anal. calcd for $C_{29}H_{36}FN_5O_5$: C, 62.91; H, 6.55; N, 12.65. Found: C, 62.60; H, 6.59; N, 12.59.

Example 16: N-({(5*S*)-3-[3-Fluoro-4-(4-{4-[4-(4-morpholinylmethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (54).

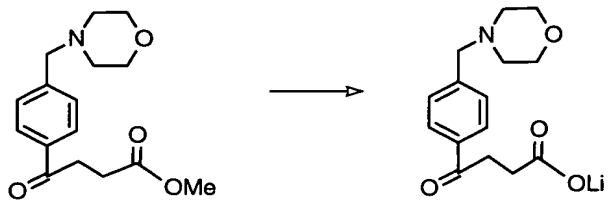
Step 1:



41 **50**

A stirred mixture of **41** (4.00 g of an 84:16 mixture of **41** and **42**, 11.8 mmol of **41**), morpholine (4.1 ml, 47 mmol), acetone 180 ml and a small amount of NaI was kept at ambient temperature for 18 h and concentrated *in vacuo*. A solution of the residue in 1N HCl was washed with Et_2O, adjusted to pH 9-10 with solid $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 3.50 g of **50**, a yellow solid: mp 79-80.5°C; MS (EI) m/z 290.6 (M^+), 260.1, 218.2, 204.7, 174.6, 89.4, 86.9; IR (drift) 1732, 1684 cm^{-1}.

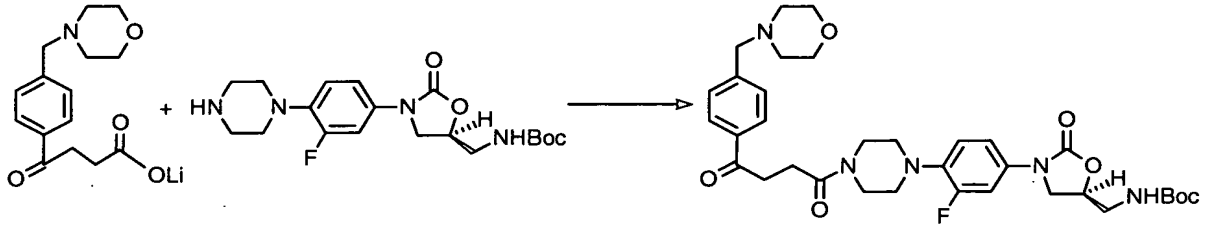
Step 2:



50 **51**

A stirred solution of **50** (3.44 g, 11.8 mmol) in MeOH (80 ml) was treated with 1N LiOH (15 ml), kept at ambient temperature for 18 h and concentrated *in vacuo*. Two 100 ml portions of Et_2O were added to the residue with concentration after each addition to give **51**, a light brown solid: MS (EI) m/z 260.6, 218.8, 204.4, 174.6, 90.3, 57.1; IR (drift) 1668 cm^{-1}.

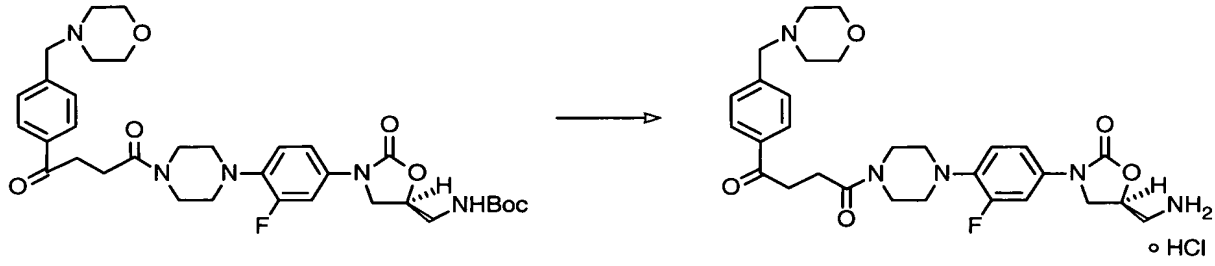
Step 3:



51 **17a** **52**

A stirred, ice cold mixture of **51** (11.8 mmol), **17a** (4.42 g, 11.2 mmol), HOBT (1.75 g, 13.0 mmol) and DMF (75 ml) was treated with EDC (4.98 g, 26.0 mmol), allowed to warm slowly to ambient temperature and stand for 3 d. It was then mixed with water (300 ml) and Et_2O (500 ml), a solid formed. The Et_2O-solid mixture was washed with water and filtered. The solid was washed with Et_2O and dried to give 5.72 g of **52**, an off-white solid: mp 128-131°C; MS (FAB) m/z 654.3 ($M+H^+$), 598.3, 393.2, 260.1, 100.1, 57.1; HRMS (FAB) calcd for $C_{34}H_{45}FN_5O_7$ ($M+H^+$) 654.3303, found 654.3289; IR (drift) 1742, 1710, 1687, 1652 cm^{-1}.

Step 4:

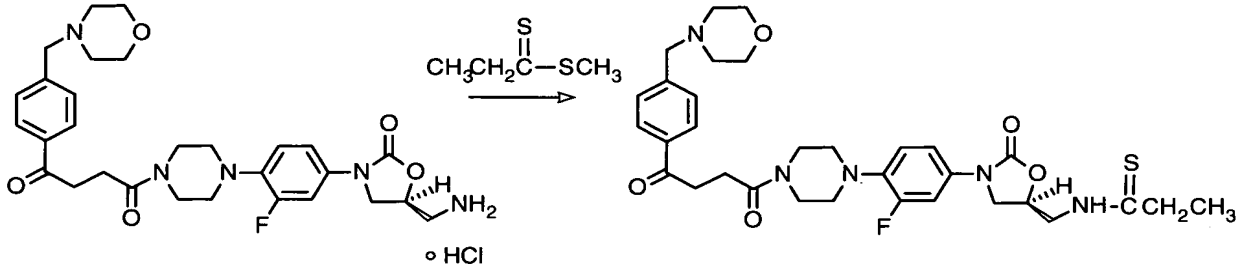


52 **53**

Solid **52** (4.00 g, 6.29 mmol) was cooled in an ice bath and treated with 4NHCl in dioxane (40 ml). The stirred mixture was kept in the ice bath for 1 h and at ambient temperature for 1 h and then concentrated *in vacuo*. Three 50 ml portions of CH_2Cl_2

were added to the residue with concentration after each addition to give **53**, an off-white solid: MS (EI) m/z 553.0 (M^+), 467.2, 454.1, 377.4, 292.2, 259.3, 174.6, 86.4; IR (drift) 1759, 1685, 1646, 1627, 1608 cm^{-1}.

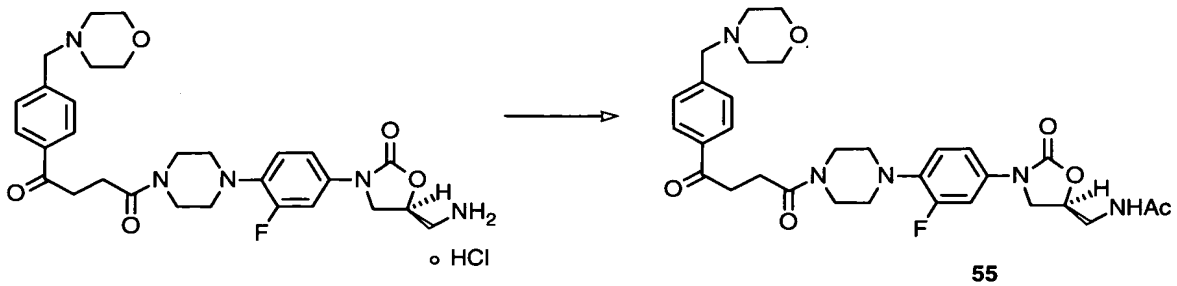
Step 5:



53 **54**

A stirred solution of **49** (one third of the product from the previous reaction – about 2.07 mmol) and triethylamine (2.31 ml, 16.6 mmol) in MeOH (28 ml) was treated with methyl dithiopropionate[5] (996 mg, 8.28 mmol) and kept at ambient temperature for 18 h. It was then concentrated *in vacuo*. The residue was mixed with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-0.25% NH_4OH-CH_2Cl_2 and crystallization of the product first from EtOAc and then EtOH gave 727 mg of **50**: mp 160°C; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.13 (t, 3H), 2.35 (s, 4H), 2.57 (q, 2H), 2.73 (m, 2H), 2.90, 3.00 (s, s, 4H), 3.22 (m, 2H), 3.55 (m, 8H), 3.66 (s, 2H), 3.79 (m, 1H), 3.90 (m, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.16 (d, 1H), 7.46 (m, 3H), 7.93 (d, 2H), 10.31 (s, 1H); MS (FAB) m/z 626.3 ($M+H^+$), 260.2, 204.2, 100.1, 86.1; IR (drift) 3250, 1743, 1683, 1647 cm^{-1}. Anal. calcd for $C_{32}H_{40}FN_5O_5S$: C, 61.42; H, 6.44; N, 11.19. Found: C, 61.26; H, 6.48; N, 11.12.

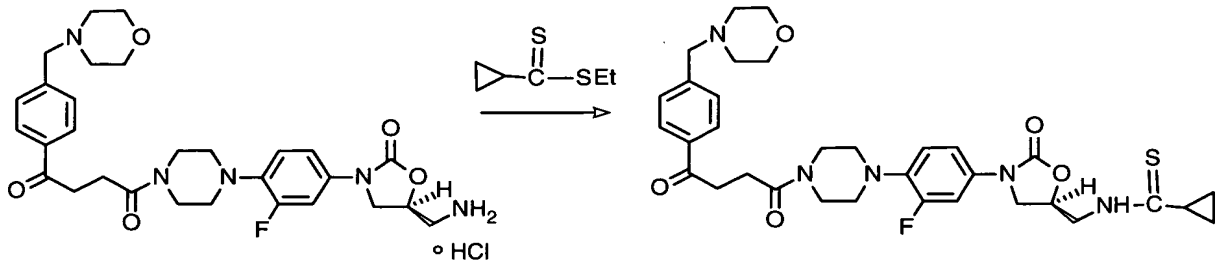
Example 17: N-({(5*S*)-3-[3-Fluoro-4-(4-{4-[4-(4-morpholinylmethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (55).



53 55

A stirred mixture of **53** (about 2.07 mmol), triethylamine (2.3 ml, 16.6 mmol), CH_2Cl_2 (21 ml) and THF (21 ml) was treated with acetyl chloride (270 mg, 3.11 mmol) and kept at ambient temperature for 18 h. It was concentrated *in vacuo* and the residue was mixed with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with mixtures of MeOH-NH_4OH-CH_2Cl_2 containing 2.5-10% MeOH and 0.25-1% NH_4OH gave the product which was crystallized from EtOH to give 835 mg of **55**: mp 178-179°C; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.82 (s, 3H), 2.34 (m, 4H), 2.73 (t, 2H), 2.90 3.00 (s, s, 4H), 3.22 (t, 2H), 3.39 (t, 2H), 3.55 (m, 8H), 3.66 (m, 3H), 4.07 (t, 1H), 4.69 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.46 (m, 3H), 7.93 (d, 2H), 8.21 (t, 1H),

Example 18: N-({(5*S*)-3-[3-Fluoro-4-(4-{4-[4-(4-morpholinylmethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide (56).



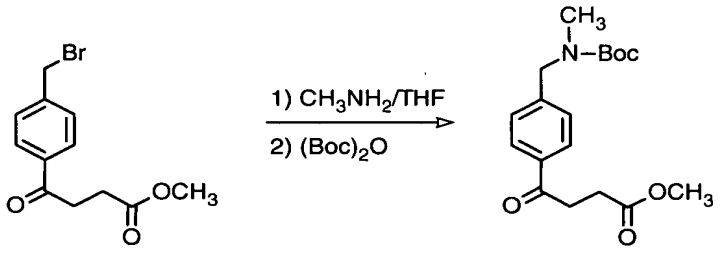
53 56

A stirred solution of **53** (about 2.07 mmol) and triethylamine (2.3 ml, 16.6 mmol) in MeOH (28 ml) was treated with ethyl cyclopropanecarbodithioate (1.21 g, 8.28

mmol), kept at ambient temperature for 18 h and concentrated *in vacuo*. A mixture of the residue in saturated $NaHCO_3$ was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-0.25% NH_4OH-CH_2Cl_2 and crystallization of the product first from EtOAc and then from EtOH gave 713 mg of **56**: mp 173-174°C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 0.84 (m, 2H), 1.02 (m, 2H), 2.15 (m, 1H), 2.35 (m, 4H), 2.73 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.22 (t, 2H), 3.55 (m, 8H), 3.66 (s, 2H), 3.79 (dd, 1H), 3.94 (m, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.18 (dd, 1H), 7.44 (d, 2H), 7.50 (dd, 1H), 7.93 (d, 2H), 10.47 (s, 1H).

Example 19: N-[((5*S*)-3-{3-Fluoro-4-[4-(4-{4-[(methylamino)methyl]phenyl}-4-oxobutanoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (60).

Step 1:

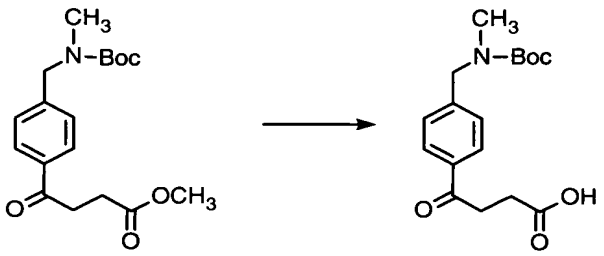


41 **57**

a) A solution of **4** (1.00 g of an 85:15 mixture of **4** and **5**) in THF (10 ml) was added to a stirred 2M solution of methylamine in THF (35 ml), kept at ambient temperature for 1 h and concentrated *in vacuo*. A solution of the residue in dilute HCl (10 ml) was washed with Et_2O and then made alkaline with solid $NaHCO_3$.

b) The mixture of step a) was treated with THF (25 ml), cooled in an ice bath and with stirring, treated with di-(*tert*-butyl)dicarbonate (998 mg, 4.58 mmol). It was allowed to warm slowly to ambient temperature and stand for 4 h. It was then extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 25% EtOAc-heptane gave 816 mg of **57**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.35, 1.42 (s, s, 9H), 2.63 (t, 2H), 2.77 (s, 3H), 3.28 (t, 2H), 3.57 (s, 3H), 4.43 (s, 2H), 7.33 (d, 2H), 7.95 (d, 2H).

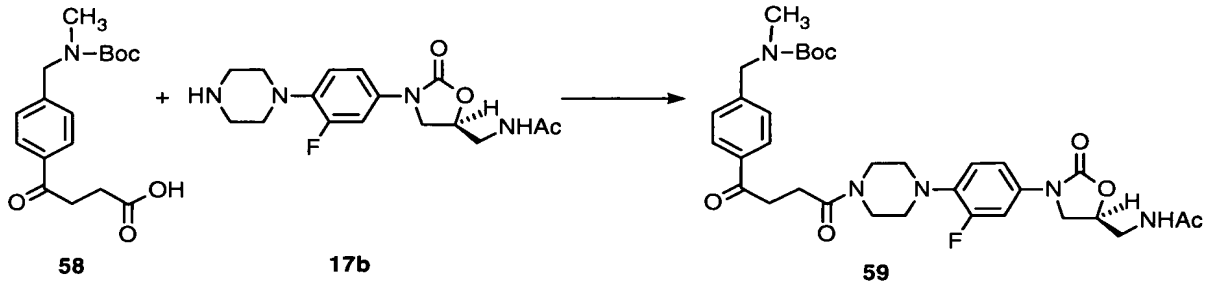
Step 2:



57 58

A stirred mixture of **53** (767 mg, 2.29 mmol), 1N LiOH (2.8 ml) and MeOH (15 ml) was kept at ambient temperature for 5 h, treated with additional LiOH (1 ml) and water (2.8 ml), kept at ambient temperature for 2h and concentrated *in vacuo* to remove MeOH. It was cooled in an ice bath, acidified with 1N HCl (4 ml) and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give 613 mg of **15**, a white foam: ^1H NMR [300 MHz, $(CD_3)_2SO$) δ 1.35, 1.41 (s, s, 9H), 2.56 (t, 2H), 2.76 (s, 3H), 3.22 (t, 2H), 4.43 (s, 2H), 7.33 (d, 2H), 7.95 (d, 2H), 12.12. (s, 1H).

Step 3:

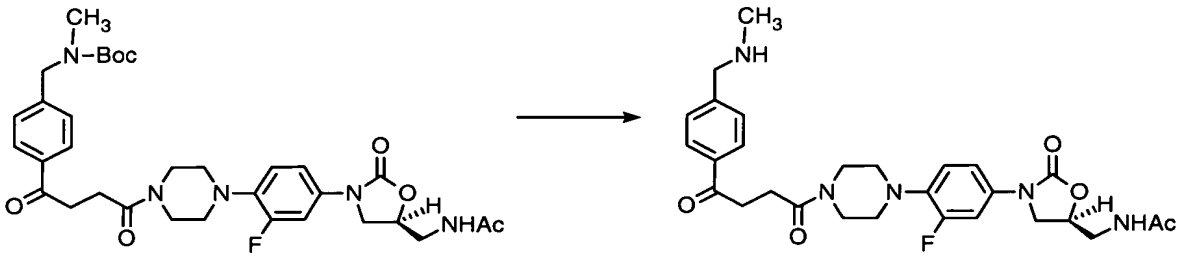


58 17b 59

An ice cold, stirred mixture of **15** (715 mg, 2.22 mmol), **16** (748 mg, 2.22 mmol), HOBT (330 mg, 2.44 mmol) and DMF (18 ml) was treated with EDC (936 mg, 4.88 mmol) and allowed to warm slowly to ambient temperature and stand for 18 h. It was concentrated *in vacuo* and the residue was chromatographed on silica gel with 4% MeOH-0.4% NH_4OH-CH_2Cl_2 to give 878 mg of **59**, a white solid: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.35, 1.42 (s,s, 9H), 1.81 (s, 3H), 2.73 (m, 2H), 2.77 (s, 3H), 2.89, 2.99 (s, s, 4H), 3.22 (m, 2H), 3.38 (m, 2H), 3.57 (s, 2H), 3.66 (m, 3H), 4.07 (t, 1H), 4.43 (s, 2H), 4.69 (m, 1H), 7.07 (t, 1H), 7.15 (d, 1H), 7.33 (d, 2H), 7.48 (d, 1H), 7.96

(d, 2H), 8.24 (m, 1H): MS (EI) m/z 639.2 (M^+), 335.1, 307.1, 306.1, 249.1, 248.1, 204.1; IR (drift) 3315, 1743, 1692, 1646 cm^{-1}.

Step 4:

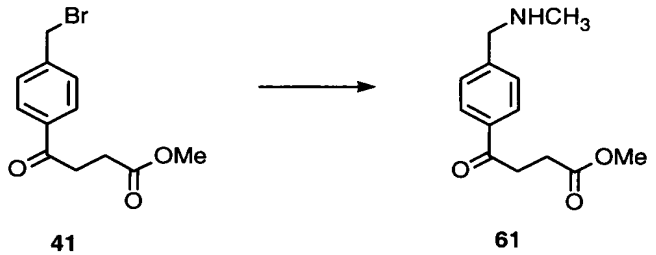


59 60

Solid **59** (616 mg, 0.963 mmol) was cooled in an ice bath and treated with 4N HCl in dioxane (10 ml). The stirred mixture was kept in the ice bath for 1 h and at ambient temperature for 30 min. It was then concentrated *in vacuo*. The residue was mixed with water (10 ml) and saturated $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from CH_2Cl_2-MeOH-hexane gave 427 mg of **60**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.24 (s, 3H), 2.72 (m, 2H), 2.89, 2.99 (s, s, 4H), 3.22 (t, 2H), 3.32 (broad s), 3.38 (t, 2H), 3.57 (s, 2H), 3.68 (m, 5H), 4.07 (t, 1H), 4.69 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.46 (m, 3H), 7.92 (d, 2H), 8.23 (t, 1H).

Example 20: N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-piperazin-1-yl]-4-oxobutanoyl}benzyl-N^1-methylglycinamide (65).

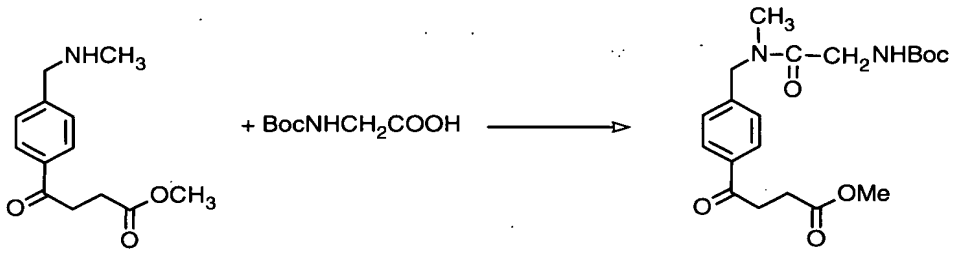
Step 1:



41 61

A solution of 41 (1.00 g of an 85:15 mixture of 41 and 42) in THF (10 ml) was added during 10 min to a stirred 2M solution of methylamine in THF (35 ml), kept at ambient temperature for 1 h and concentrated *in vacuo*. A solution of the residue in dilute HCl was washed with Et_2O and then made alkaline with solid $NaHCO_3$. It was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 538 mg of 41: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 2.23 (s, 3H), 2.63 (t, 2H), 3.27 (t, 2H), 3.57 (s, 3H), 3.69 (s, 2H), 7.44 (d, 2H), 7.91 (d, 2H); MS (EI) m/z 235.1 (M^+), 205.1, 204.1, 162.1, 148.1, 120.0; IR (drift) 3331, 1738, 1685 cm^{-1}.

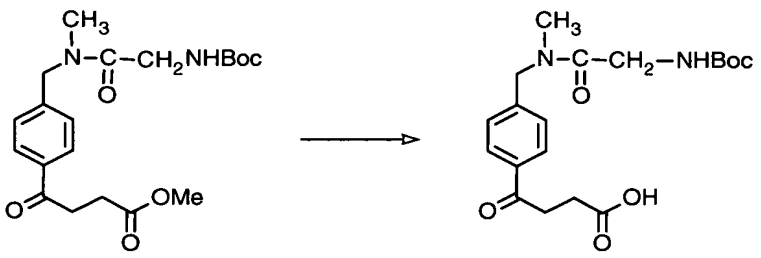
Step 2:



61 62

A stirred, ice cold solution of 61 (509 mg, 2.16 mmol), N-*t*-Boc-glycine (378 mg, 2.16 mmol) and HOBT (321 mg, 2.38 mmol) in DMF (18 ml) was treated with EDC (912 mg, 4.76 mmol), warmed slowly to ambient temperature and kept for 18 h. It was concentrated *in vacuo* and the residue was mixed with water and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 40-50% EtOAc-heptane gave 765 mg of 62, an oil: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34, 1.37 (s, s, 9H), 2.63 (t, 2H), 2.81, 2.90 (s, s, 3H), 3.28 (t, 2H), 3.57 (s, 3H), 3.76, 3.84 (d, d, 2H), 4.56, 4.62 (s, s, 2H), 6.80 (m, 1H), 7.33 (d, 2H), 7.92, 7.98 (d, d, 2H); IR (drift) 3419, 3362, 1737, 1714, 1687, 1658 cm^{-1}.

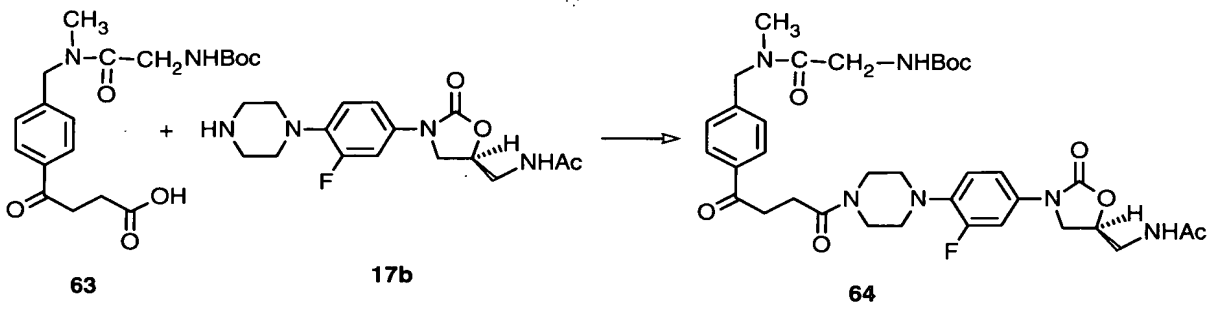
Step 3:



62 63

A stirred mixture of **62** (701 mg, 1.79 mmol) and MeOH (12 ml) was treated with 1N LiOH (2.2 ml) and kept at ambient temperature for 5 h. Additional water (2.2 ml) and LiOH (1 ml) were added and the mixture was kept at ambient temperature for about 6 h and concentrated to remove MeOH. This mixture was cooled in an ice bath, acidified with 1N HCl and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give 616 mg of **63**, a white foam: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34, 1.37 (s, s, 9H), 2.55 (t, 2H), 2.80, 2.90 (s, s, 3H), 3.21 (t, 2H), 3.77, 3.84 (d, d, 2H), 4.56, 4.62 (s, s, 2H), 6.81 (m, 1H), 7.33 (d, 2H), 7.92, 7.97 (d, d, 2H).

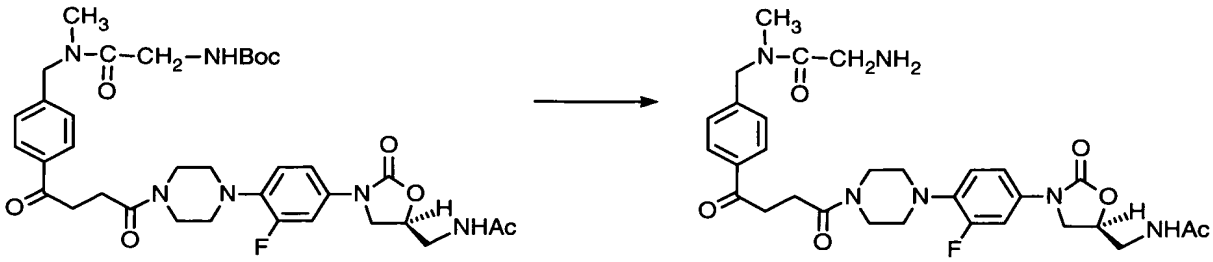
Step 4:



63 **17b** **64**

An ice cold, stirred mixture of **63** (555 mg, 1.47 mmol), **17b** (493 mg, 1.47 mmol), HOBT (219 mg, 1.62 mmol) and DMF (12 ml) was treated with EDC (620 mg, 3.23 mmol), allowed to warm slowly to ambient temperature and kept for 18 h. It was concentrated *in vacuo* and the residue was chromatographed on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2. The product was crystallized from CH_2Cl_2-MeOH-hexane to give 756 mg of **64**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34, 1.37 (s, s, 9H), 1.81 (s, 3H), 2.73 (m, 2H), 2.81, 2.90 (s, s, 3H), 2.90, 2.99 (s, s, 4H), 3.21 (m, 2H), 3.38 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.68 (m, 1H), 3.78, 3.84 (d, d, 2H), 4.07 (t, 1H), 4.57, 4.63 (s, s, 2H), 4.70 (m, 1H), 6.81 (m, 1H), 7.07 (t, 1H), 7.15 (dd, 1H), 7.33 (d, 2H), 7.49 (dd, 1H), 7.93, 7.98 (d, d, 2H), 8.23 (t, 1H); MS (FAB) m/z 697 ($M+H^+$), 696 (M^+), 597.3, 337.1, 261.1, 204.1; HRMS (FAB) calcd for $C_{35}H_{45}FN_6O_8$ (M^+) 696.3282, found 696.3293.

Step 5:

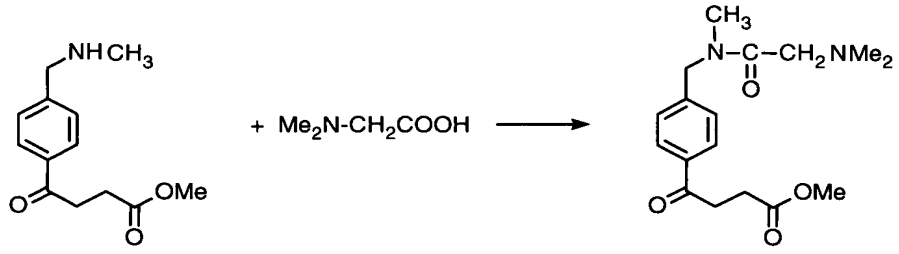


64 65

Solid **64** (400 mg, 0.574 mmol) was cooled in an ice bath and treated with 4N HCl in dioxane (10 ml). The stirred mixture was kept in the ice bath for 1 h and at ambient temperature for 30 min and then concentrated *in vacuo*. A mixture of the residue in water (10 ml) and saturated $NaHCO_3$ (10 ml) was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from CH_2Cl_2-EtOAc-hexane gave 281 mg of **65**: MS (EI) m/z 596 (M^+), 552.3, 510.3, 495.3, 336.2, 306.2, 294.2, 250.3, 151.1; IR (drift) 3541, 3372, 3326, 1743, 1686, 1646 cm^{-1}. Anal. calcd for $C_{30}H_{37}FN_6O_6$: C, 60.39; H, 6.25; N, 14.09. Found: C, 60.08; H, 6.88; N, 13.75.

Example 21: N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)-N^1,N^2,N^2-trimethylglycinamide (68).

Step 1:

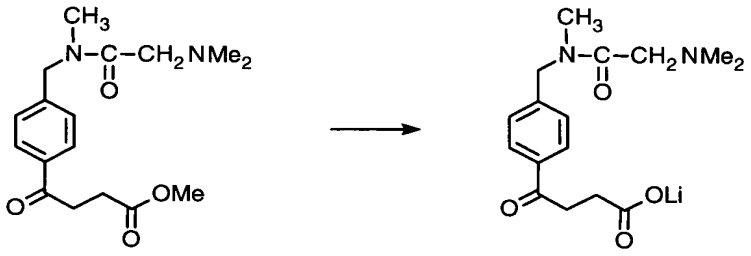


61 62

A stirred, ice cold mixture of **61** (509 mg, 2.16 mmol), HOBT (321 mg, 2.38 mmol), N,N-dimethylglycine (222 mg, 2.16 mmol) and DMF (18 ml) was treated with EDC (912 mg, 4.76 mmol) and allowed to warm slowly to ambient temperature. It was kept at this temperature for 18 h and concentrated *in vacuo*. The residue was chromatographed on silica gel with 4% MeOH-0.4% NH_4OH-CH_2Cl_2 to give 578 mg

of **62**, a yellow oil: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 2.15, 2.20 (s, s, 6H), 2.63 (t, 2H), 2.74, 2.97 (s, s, 3H), 3.08, 3.13 (s, s, 2H), 3.27 (t, 2H), 3.57 (s, 3H), 4.54, 4.74 (s, s, 2H), 7.34 (m, 2H), 7.95 (m, 2H); MS (EI) m/z 320.1 (M^+), 289.1, 205.0, 146.0, 119.0, 118.0.

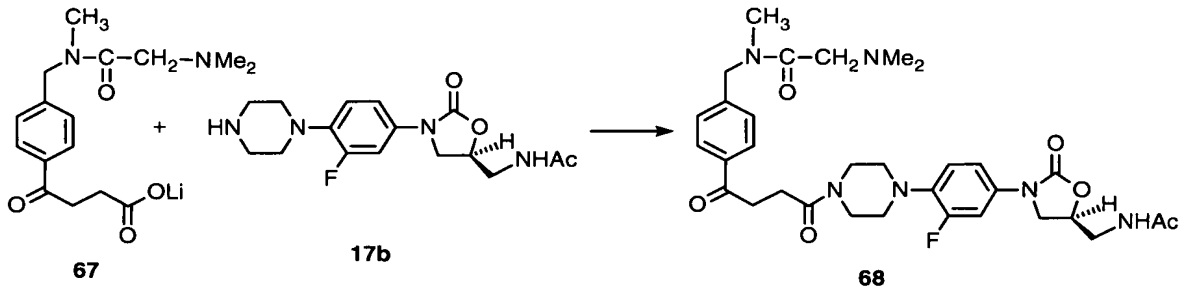
Step 2:



66 **67**

A stirred mixture of **66** (541 mg, 1.69 mmol), 1M lithium hydroxide (2.0 ml) and MeOH (11 ml) was kept at ambient temperature for 18 h, treated with additional LiOH (0.5 ml) and kept ambient temperature for 8 h. It was concentrated to dryness *in vacuo* and the residue was triturated with Et_2O to give **67** a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 2.15, 2.19 (s, s, 6H), 2.24 (t, 3H), 2.73, 2.95 (s, s, 3H), 3.07 (m, 4H), 3.39 (s, 3H), 4.52, 4.72 (s, s, 2H), 7.29 (m, 2H), 7.89 (m, 2H); MS (FAB) m/z 313 ($M+H^+$); HRMS (FAB) calcd for $C_{16}H_{22}LiN_2O_4$ ($M+H^+$) 313.1739, found 313.1739.

Step 3:



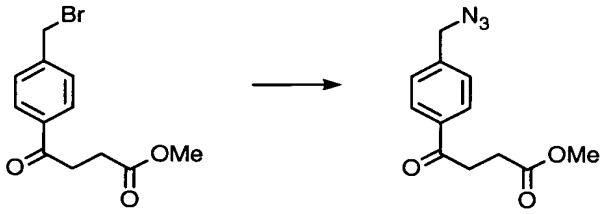
67 **17b** **68**

A stirred, ice cold mixture of **67** (468 mg, 1.50 mmol), **17b** (505 mg, 1.50 mmol), HOBT (223 mg, 1.65 mmol) and DMF (12 ml) was treated with EDC (633 mg, 3.30 mmol) and allowed to warm slowly to ambient temperature. It was kept at this temperature for 24 h and concentrated *in vacuo*. The residue was mixed with water and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated.

Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ and crystallization of the product from EtOAc-CH_2Cl_2-hexane gave 638 mg of **68**, a white solid: MS (EI) m/z 580.4, 565.3, 552.3, 335.2, 306.2; MS (CI) m/z 625 ($M+H^+$); IR (drift) 3306, 1743, 1688, 1645 cm^{-1}. Anal. calcd for $C_{32}H_{41}FN_6O_6$: C, 61.52; H, 6.61; N, 13.45. Found: C, 61.10; H, 6.71; N, 13.32.

Example 22: N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)-N^2,N^2-dimethylglycinamide (75).

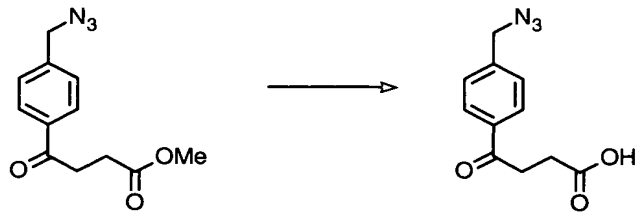
Step 1:



41 **69**

A stirred mixture of **41** (16.7 g of a 9:1 mixture of **41** and **42**), sodium azide (22.3 g, 343 mmol) and DMF (84 ml) was warmed at 40-45°C for 4 h and diluted with EtOAc (200 ml). It was washed with water, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 10-30% EtOAc-5% CH_2Cl_2-heptane gave 12.1 g of **69**: mp 29-30°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (t, 2H), 3.32 (t, 2H), 3.71(s, 3H), 4.42 (s, 2H), 7.42 (d, 2H), 8.00 (d, 2H); MS (EI) m/z 247.0 (M^+), 216.0, 205.0, 160.0, 132.0, 104.0; IR (drift) 2103, 1735, 1686 cm^{-1}.

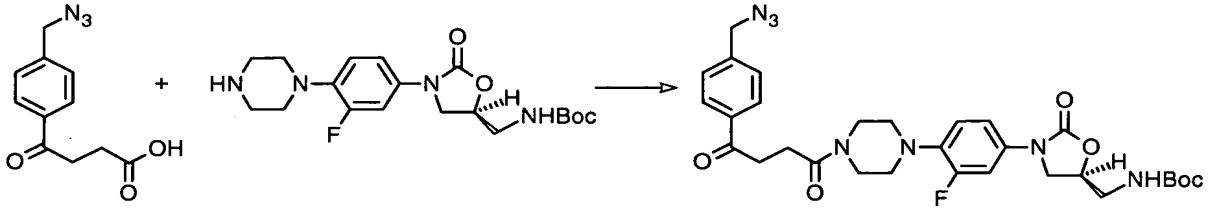
Step 2:



69 70

A stirred mixture of **23** (12.0 g, 48.5 mmol) and MeOH (320 ml) was treated with 1N LiOH (53.4 ml) and kept at ambient temperature for 21 h. Additional LiOH (2.6 ml) was added and the mixture was kept at ambient temperature for 4 h and concentrated *in vacuo* to remove MeOH. The resulting aqueous solution was acidified with 1N HCl and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Trituration of the residue with 10% EtOAc-heptane (100 ml) gave 10.04 g of **24**: ^1H NMR (300 MHz, $CDCl_3$) δ 2.82 (t, 2H), 3.32 (t, 2H), 4.43 (s, 2H), 7.42 (d, 2H), 8.00 (d, 2H).

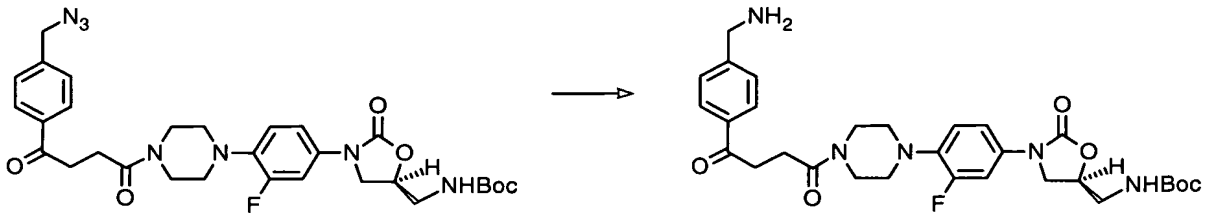
Step 3:



70 17a 71

An ice cold, stirred mixture of **70** (10.0 g, 42.9 mmol), **17a** (16.92 g, 42.9 mmol), HOBT (6.38 g, 47.2 mmol), and DMF (377 ml) was treated with EDC (18.1 g, 94.4 mmol) and kept for 4 h. It was diluted with water (1 L) and mixed with 1:1 Et_2O-heptane (500 ml). The solid was collected by filtration, washed with water and heptane and dried. Recrystalization from CH_2Cl_2-heptane gave 20.0 g of **71**: mp 160-160.5°C; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34 (s, 9H), 2.74 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.24 (m, 4H), 3.58, 3.66 (s, s, 4H), 3.74 (dd, 1H), 4.07 (t, 1H), 4.56 (s, 2H), 4.66 (m, 1H), 7.07 (t, 1H), 7.17 (m, 2H), 7.49 (m, 3H), 8.00 (d, 2H); MS (EI) m/z 609.2 (M^+), 308.1, 165.0, 153.1, 138.0, 137.0; IR (drift) 3376, 2132, 2095, 1788, 1732, 1685, 1652 cm^{-1}.

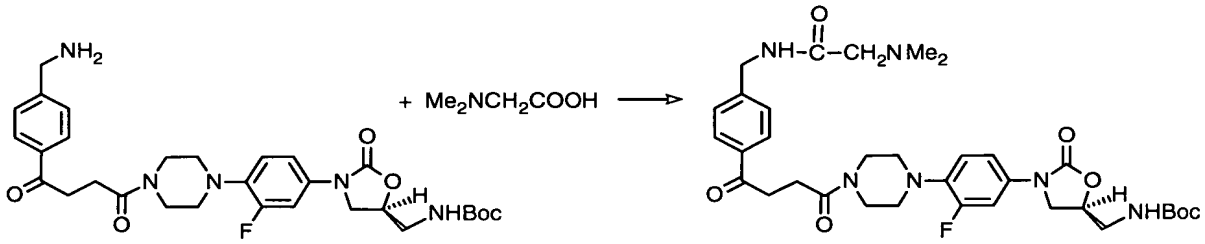
Step 4:



71 72

A mixture of 71 (4.97 g, 8.15 mmol), 10% palladium-on-carbon catalyst (1.25 g) and THF (300 ml) was hydrogenated at an initial pressure of 45 psi for 1.5 h. The flask was evacuated and refilled with hydrogen (45 psi) and the reaction was continued for 2 h. The mixture was filtered through celite; the solid was washed well with THF and the filtrate was concentrated *in vacuo* to give 4.95 g of **72**, a white foam: IR (drift) 3320, 1753, 1710, 1684, 1645 cm^{-1}.

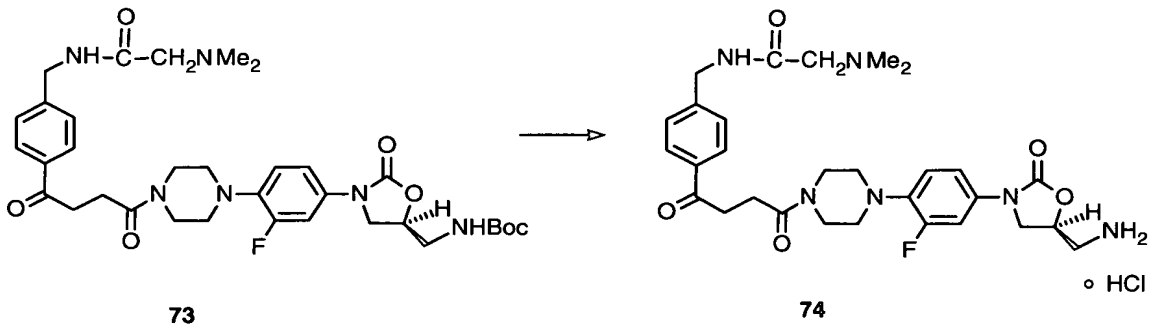
Step 5:



72 73

An ice cold, stirred mixture of **72** (2.00 g, 3.43 mmol), N,N-dimethylglycine (354 mg, 3.43 ml), HOBT (510 mg, 3.77 mmol) and DMF (30 ml) was treated with EDC (1.45 g, 7.55 mmol) and kept for 3 h. It was then diluted with water (50 ml) and extracted (emulsions) with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-CH_2Cl_2 gave 473 mg of **73**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.33 (s, 9H), 2.21 (s, 6H), 2.72 (m, 2H), 2.89, 2.99 (s, s, 4H), 2.93 (s, 2H), 3.23 (m, 4H), 3.57, 3.66 (s, s, 4H), 3.74 (dd, 1H), 4.06 (t, 1H), 4.33 (d, 2H), 4.67 (m, 1H), 7.07 (t, 1H), 7.18 (m, 2H), 7.37 (d, 2H), 7.47 (dd, 1H), 7.92 (d, 2H), 8.41 (t, 1H).

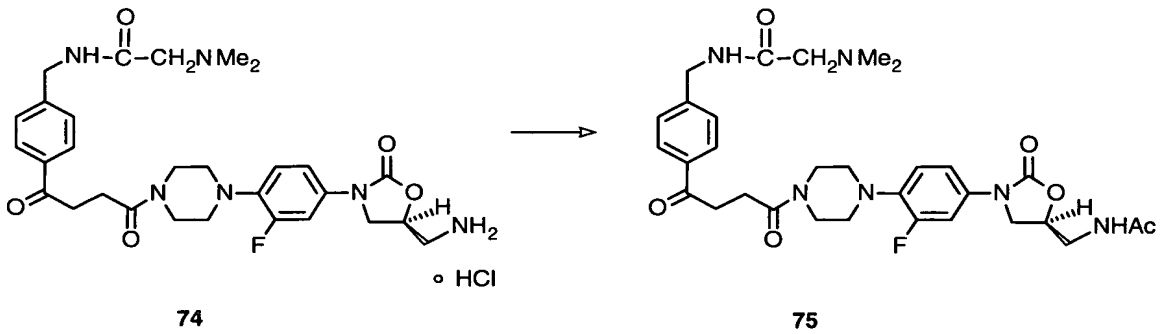
Step 6:



73 74

Solid **73** (356 mg, 0.532 mmol) was cooled in an ice bath and treated with 4N HCl in dioxane (10 ml). The stirred mixture was kept in the ice bath for 2 h and at ambient temperature for 1 h and then concentrated *in vacuo*. Four portions of CH_2Cl_2 (25 ml) were added to the residue with concentration after each addition to give 451 mg of **74**, as an off-white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 2.73 (m, 2H), 2.79, 2.81 (s, s, 6H), 2.90, 3.00 (s, s, 4H), 3.22 (m, 4H), 3.54, 3.66 (s, s, 4H), 3.86 (dd, 1H), 4.01 (d, 2H), 4.14 (t, 1H), 4.41 (d, 2H), 4.95 (m, 1H), 6.22 (broad s, 4H), 7.15 (m, 2H), 7.42 (d, 2H), 7.48 (dd, 1H), 7.94 (d, 2H), 8.49 (s, 3H), 9.36 (t, 1H), 10.02 (broad s, 1H).

Step 7:

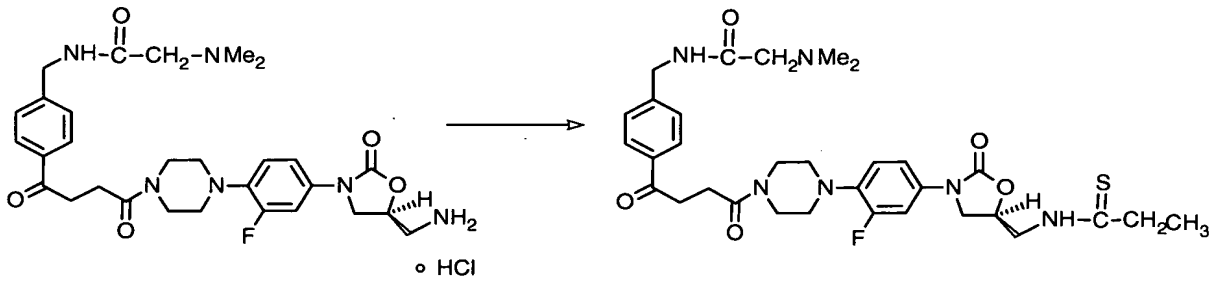


74 75

A stirred, ice cold solution of **74** (about 0.357 mmol) in pyridine (8 ml) was treated with acetic anhydride (47 μL, 0.497 mmol) and allowed to warm to ambient temperature during 1 h. It was kept at ambient temperature for 1 h and concentrated *in vacuo*. Chromatography of the residue on silica gel first with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and then with 2.5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH gave 56 mg of **75**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] 1.81 (s, 3H), 2.20 (s, 6H), 2.72 (t, 2H), 2.91 (m, 4H), 2.99 (s, 2H), 3.21 (t, 2H), 3.38 (t, 2H), 3.57 (s, 2H), 3.66 (m, 3H), 4.07 (t, 1H), 4.33 (d, 2H), 4.69 (m, 1H), 7.07 (t, 1H)

7.16 (dd, 1H), 7.37 (d, 2H), 7.48 (dd, 1H), 7.91 (d, 2H), 8.23 (t, 1H), 8.40 (t, 1H); MS (EI) m/z 610.2 (M^+), 335.1, 306.1, 106.1; HRMS calcd for $C_{31}H_{40}FN_6O_6$ ($M+H^+$) 611.2993, found 611.2996.

Example 23: N^1-(4-{4-[4-[2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)-N^2,N^2-dimethylglycinamide (76).

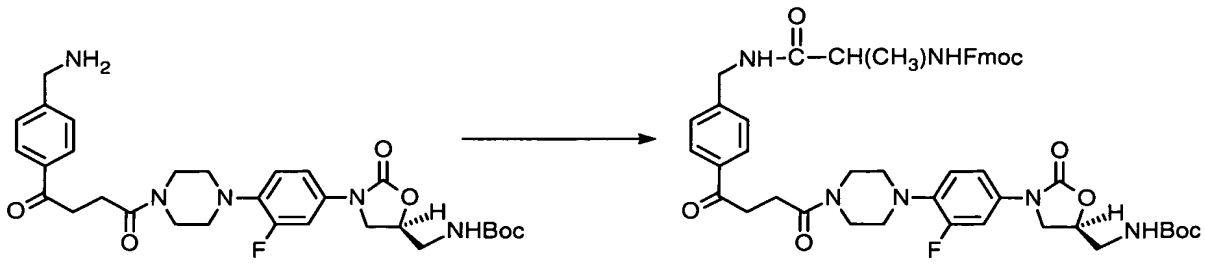


74 76

A stirred solution of 74 (270 mg, about 0.318 mmol) in MeOH (15 ml) was cooled in an ice bath and treated with Et_3N (0.46 ml, 3.31 mmol) and ethyl dithiopropionate (111 mg, 0.828 mmol). It was kept at ambient temperature for 18 h, adsorbed on silica gel (2 g) and chromatographed on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2. The product was crystallized from MeOH-acetone-Et_2O to give 130 mg of 76, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.12 (t, 3H), 2.57 (q, 2H), 2.73 (t, 2H), 2.80 (s, 6H), 2.89, 3.00 (s, s, 4H), 3.22 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.80 (dd, 1H), 3.89 (m, 2H), 4.00 (s, 2H), 4.11 (t, 1H), 4.42 (d, 2H), 4.94 (m, 1H), 7.07 (t, 1H), 7.18 (dd, 1H), 7.42 (d, 2H), 7.48 (dd, 1H), 7.94 (d, 2H), 9.27 (t, 1H), 9.90 (s, 1H), 10.40 (t, 1H).

Example 24a: (*S*)-N^1-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)alaninamide (80).

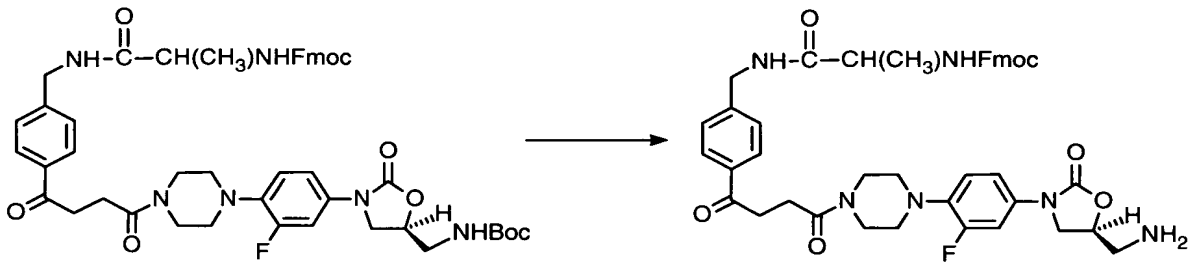
Step 1:



72 77

An ice cold, stirred solution of **72** (1.44 g, 2.46 mmol) and Hunig's base (0.48 ml, 2.71 mmol) in CH_2Cl_2 (25 ml) and THF (25 ml) was treated with N-Fmoc-L-alanyl chloride (894 mg, 2.71 mmol) and kept in the ice bath for 1 h. The solid mixture was mixed with additional CH_2Cl_2 (15 ml) and kept at ambient temperature for 18 h. It was then treated with about 20 ml of heptane and filtered to give 1.672 g of **29**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.25 (d, 3H), 1.34 (s, 9H), 2.71 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.23 (m, 4H), 3.57, 3.66 (s, s, 4H), 3.74 (dd, 1H), 4.06 (m, 2H), 4.24 (m, 3H), 4.34 (d, 2H), 4.66 (m, 1H), 7.07 (t, 1H), 7.18 (m, 2H), 7.35 (m, 6H), 7.48 (dd, 1H), 7.58 (d, 1H), 7.72 (m, 2H), 7.89 (m, 4H), 8.48 (t, 1H).

Step 2:

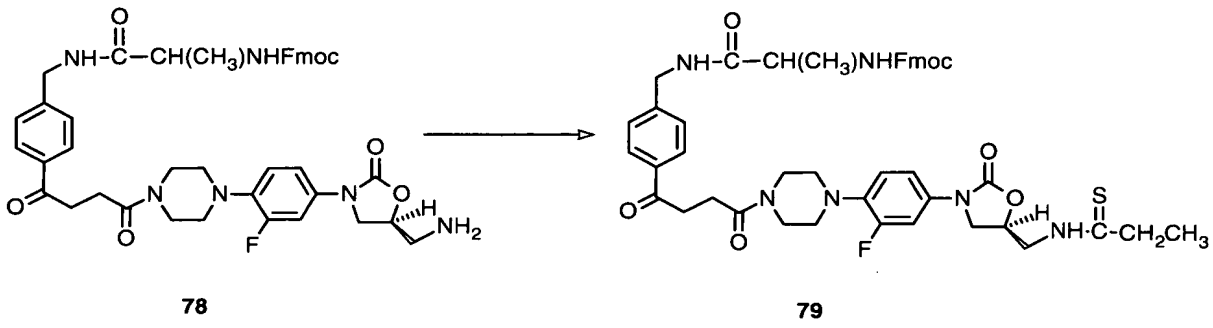


77 78

Solid **77** (940 mg, 1.07 mmol) was cooled in an ice bath and treated with 4N HCl in dioxane (10 ml). The mixture was stirred in the ice bath for 1 h and at ambient temperature for 1 h and concentrated *in vacuo*. The residue was mixed with four 25 ml portions of CH_2Cl_2 with concentration after each addition to give a white solid. A mixture of this material in saturated $NaHCO_3$ (20 ml) was extracted first with CH_2Cl_2 then with 5% MeOH-CH_2Cl_2 and finally with EtOAc. The extracts were dried and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5%

NH_4OH-$CHCl_3$ gave 562 mg of **78**, a white solid: MS (ESI) m/z 777.4 ($M+H^+$), 577.1, 484.2; IR (drift) 3283, 1749, 1682, 1650, 1608 cm^{-1}.

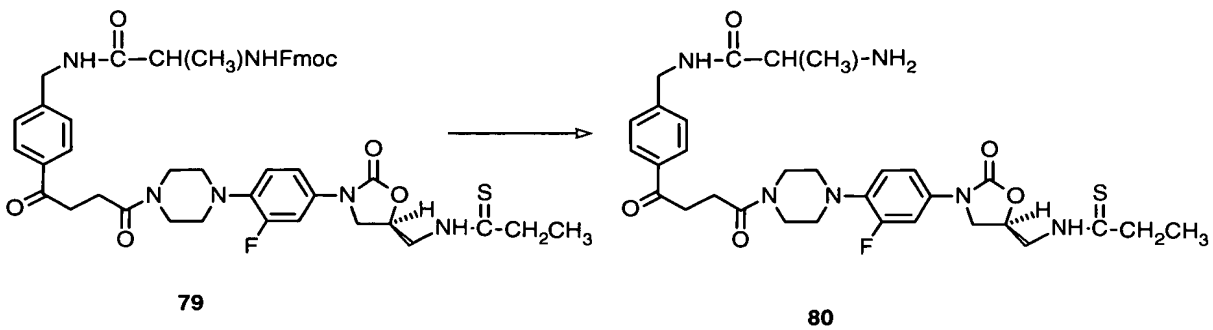
Step 3:



78 **79**

A stirred mixture of **78** (641 mg, 0.825 mmol), triethylamine (0.29 ml, 2.07 mmol), ethyl dithiopropionate (155 mg, 1.16 mmol), MeOH (15 ml) and CH_2Cl_2 (5 ml) was kept at ambient temperature for 3 h. Additional triethylamine (0.2 ml) and dithioester (100 mg) were added and the reaction was continued for an additional 2 h. The mixture was then mixed with CH_2Cl_2 (50 ml) and silica gel (2 g) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-CH_2Cl_2 and trituration of the product with a mixture of EtOAc-MeOH-CH_2Cl_2-Et_2O gave 400 mg of **79**, a white solid: MS (ESI) m/z 849.0 ($M+H^+$), 871.0 ($M+Na^+$), 887.0 ($M+K^+$); IR (drift) 3305, 1759, 1688, 1676, 1654, 1635 cm^{-1}.

Step 4:



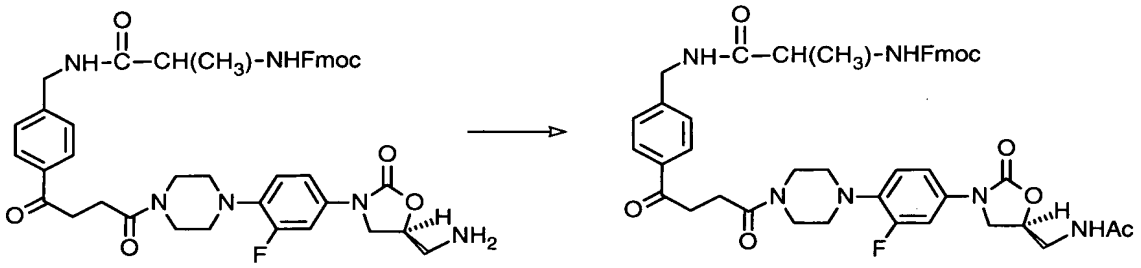
79 **80**

A stirred mixture of **79** (380 mg, 0.448 mmol), trisamine resin (400 mg, 1.6 mmol) and THF (100 ml) was refluxed for 5 d. Additional resin (250 mg) was added and the mixture was refluxed for 8 h and filtered. The filtrate was treated with silica gel (2 g) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5%

NH_4OH-$CHCl_3$ and crystallization of the product from EtOAc-MeOH-heptane gave 228 mg of **80**, a white solid: MS (FAB) m/z 627.3 ($M+H^+$), 261.1; HRMS (FAB) calcd for $C_{31}H_{40}FN_6O_5S$ ($M+H^+$) 627.2765, found 627.2767; IR (drift) 3317, 3286, 1761, 1672, 1648, 1633 cm^{-1}. Anal. calcd for $C_{31}H_{39}FN_6O_5S$: C, 59.41; H, 6.27; N, 13.41. Found: C, 58.58; H, 6.18; N, 13.15.

Example 24b: (*S*)-N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-2-oxobutanoyl}benzyl)alaninamide (82).

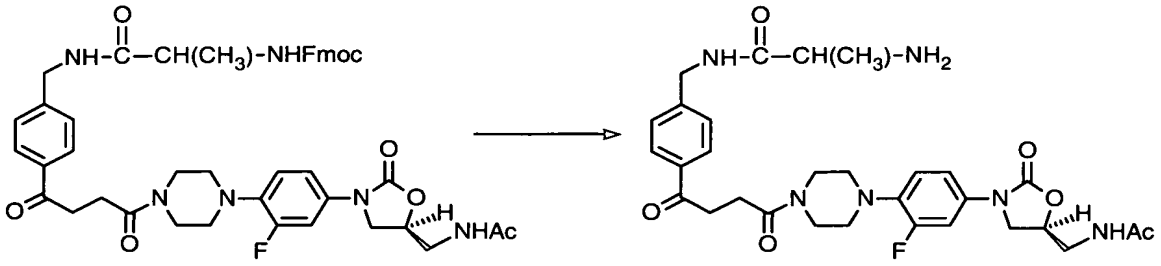
Step 1:



78 **81**

A stirred mixture of **78** (500 mg, 0.644 mmol), triethylamine (0.72 ml, 5.15 mmol), CH_2Cl_2 (6.5 ml) and THF (6.5 ml) was treated with acetyl chloride (84 μL, 0.966 mmol) and kept at ambient temperature for 2 h. Additional acetyl chloride (45 μL) was added and the mixture was kept at ambient temperature for 18 h. It was then treated with silica gel (1.5 g) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-CH_2Cl_2 gave the product (370 mg) which was further purified by preparative TLC on silica gel with 2.5% MeOH-CH_2Cl_2 to give 323 mg of **81**, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.25 (d, 3H), 1.82 (s, 3H), 2.72 (m, 2H), 2.90, 3.00 (s, s, 4H), 3.14 (m, 2H), 3.38 (t, 2H), 3.62 (m, 5H), 4.07 (m, 2H), 4.25 (m, 3H), 4.33 (d, 2H), 4.70 (m, 1H), 7.30 (m, 10H), 7.72 (m, 2H), 7.89 (m, 4H), 8.21 (t, 1H), 8.47 (t, 1H).

Step 2:

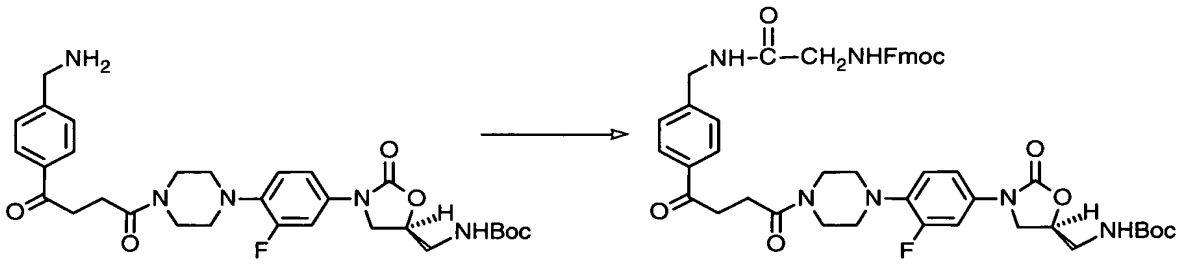


81 82

A stirred mixture of **81** (300 mg, 0.366 mmol), trisamine resin (91 mg) and THF (30 ml) was refluxed for 2 h and treated with additional resin (100 mg). It was refluxed for 18 h, treated with additional resin (200 mg) and refluxed for 8 h. Additional resin (200 mg) was again added and the mixture was refluxed for 18 h. The reaction was now complete; the mixture was filtered and the filtrate was concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ and crystallization of the product from Et_2O-EtOAc-heptane gave 151 mg of **82**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.14 (d, 3H), 1.81 (s, 3H), 2.26 (broad s, 2H), 2.72 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.21 (t, 2H), 3.00 (m, 1H), 3.38 (t, 2H), 3.63 (m, 5H), 4.07 (t, 1H), 4.33 (d, 2H), 4.68 (m, 1H), 7.07 (t, 1H), 7.15 (dd, 1H), 7.37 (d, 2H), 7.49 (dd, 1H), 7.92 (d, 2H), 8.21 (t, 1H), 8.40 (t, 1H).

Example 25: N^1-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)glycinamide (85).

Step 1:

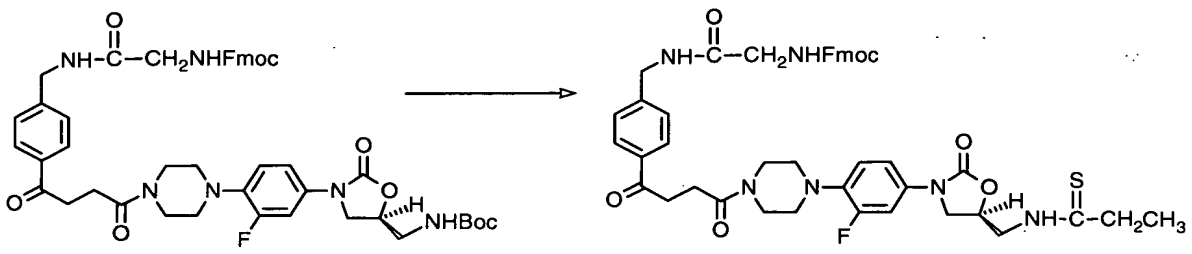


72 83

An ice cold, stirred mixture of **72** (957 mg, 1.64 mmol), diisopropylethylamine

(Hunig's base, HB, 0.316 ml, 1.77 mmol) and THF (33 ml) was treated, portionwise during about 1 min, with Fmoc glycyl chloride (559 mg, 1.77 mmol). The mixture was allowed to warm slowly to ambient temperature and stand for 18 h. It was then concentrated *in vacuo*, and the residue was chromatographed on silica gel with 3% MeOH-CH_2Cl_2. Impure fractions were triturated with EtOAc-heptane and rechromatographed with 2.5% MeOH-CH_2Cl_2. The product was crystallized from EtOAc-heptane to give 600 mg of **83**: MS (ESI) m/z 862.9 ($M+H^+$), 885.0 ($M+Na^+$); IR (drift) 3353, 3329, 1741, 1728, 1710, 1691, 1682, 1652 cm^{-1}.

Step 2:

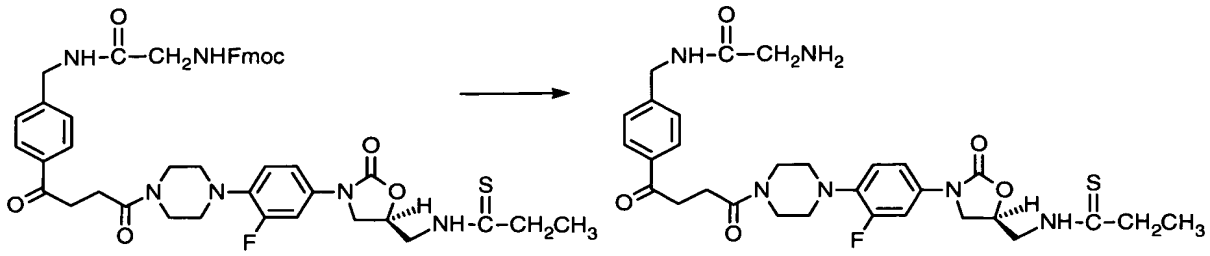


83 **84**

a) Ice cold, stirred 4N HCl in dioxane (10 ml) was treated, portionwise during 2 min with **83** (500 mg, 0.579 mmol). The mixture was kept in the ice bath for 1 h and at ambient temperature for 1 h and then concentrated *in vacuo*. The residue was triturated with three 50 ml portions of CH_2Cl_2 with concentration after each addition to give a white solid: MS (EI) m/z 762.5 (M^+); IR (drift) 3289, 3240, 1762, 1726, 1716, 1676, 1663, 1657, 1645, 1632, 1628, 1608 cm^{-1}.

b) A mixture of the solid of step a) (463 mg), triethylamine (242 µL, 1.74 mmol), ethyl dithiopropionate (93 mg, 0.695 mmol) and MeOH (10 ml) was stirred at ambient temperature for 18 h. Additional MeOH (5 ml), triethylamine (242 µL) and dithioester (93 mg) were added to the mixture which was stirred for an additional 24 h. It was warmed at 50°C for 1.5 h then diluted with CH_2Cl_2 (15 ml) and stirred at ambient temperature for 4 h. This mixture was diluted with CH_2Cl_2 (100 ml) adsorbed on silica gel and chromatographed on silica gel with 3.5% MeOH-CH_2Cl_2. The product was crystallized from EtOAc-CH_2Cl_2-heptane to give 218 mg of **84**, as a white powder: MS (ESI) m/z 835.0 ($M+H^+$), 857.0 ($M+Na^+$); IR (drift) 3287, 1753, 1749, 1743, 1728, 1710, 1691, 1680, 1663, 1656, 1645, 1639, 1635 cm^{-1}.

Step 3:

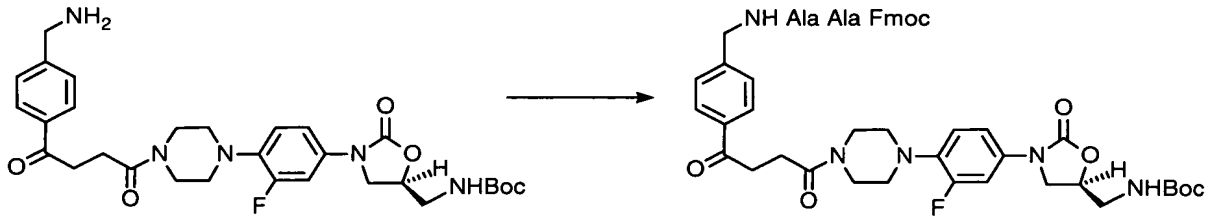


84 85

A stirred solution of **84** (150 mg, 0.180 mmol) in DMF (1.8 ml) was treated with piperidine (45 µL), kept at ambient temperature for 30 min and concentrated *in vacuo*. The residue was chromatographed on silica gel with 5% MeOH-CH_2Cl_2. The resulting product was combined with the product from a similar 0.0599 mmol reaction and rechromatographed on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$. Crystallization of the product from Et_2O-CH_2Cl_2 gave 74.8 mg of **85**: MS (EI) m/z 612.5 (M^+), 568.3, 511.2, 321.6, 280.1, 259.1, 247.0, 208.4, 191.5, 164.4; HRMS (FAB) calcd for $C_{30}H_{38}FN_6O_5S$ ($M+H^+$) 613.2608, found 613.2607.

Example 26: (*S*)-Alanyl-(*S*)-N^1-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)alaninamide (89).

Step 1:

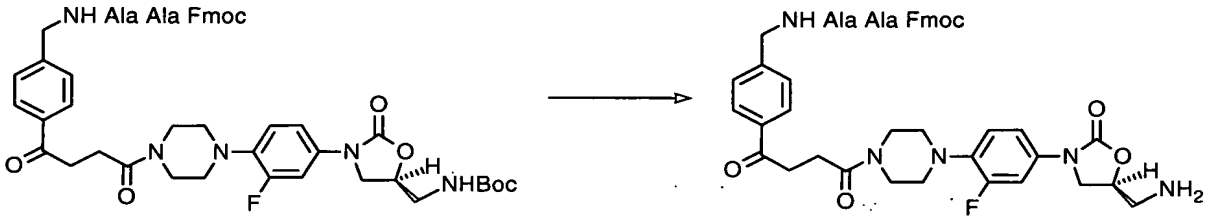


72 86

A stirred, ice cold mixture of **72** (2.00 g, 3.43 mmol), HOBT (510 mg, 3.77 mmol), N-Fmoc-L-alanyl-L-alanine (1.31 g, 3.43 mmol) and DMF (30 ml) was treated with EDC (1.45 g, 7.54 mmol) and allowed to warm slowly to ambient temperature. It was

kept at ambient temperature for 4 h and diluted with about 500 ml of water. The resulting solid was collected by filtration, dried and chromatographed on silica gel with 5% MeOH-CH_2Cl_2 to give 2.22 g of **86**: MS (ESI) m/z 948.0 ($M+H^+$), 970.0 ($M+Na^+$), 985.9 ($M+K^+$); IR (drift) 3305, 1744, 1733, 1710, 1690, 1683, 1694, 1640 cm^{-1}.

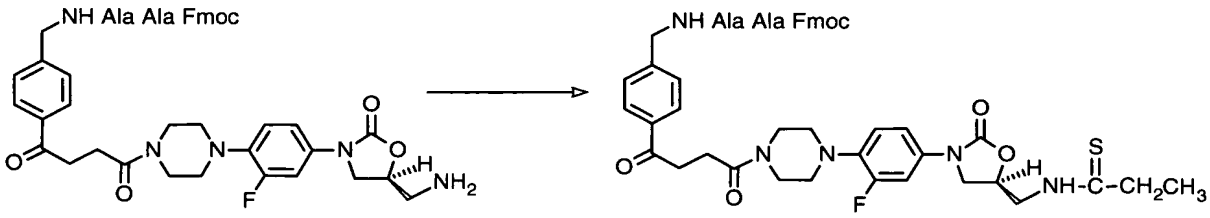
Step 2:



86 **87**

Stirred, ice cold 4N HCl in dioxane (20 ml) was treated with **72** (2.21 g, 2.33 mmol) and the mixture was kept in the ice bath for 2 h and at ambient temperature for 1 h. It was then concentrated *in vacuo* and the residue was triturated with three 50 ml portions of CH_2Cl_2 with concentration after each addition. A mixture of the residue in saturated $NaHCO_3$ was extracted with CH_2Cl_2. A solid that formed during this process was collected by filtration, washed with water and dissolved in 20% MeOH-CH_2Cl_2. The organic solutions were dried ($MgSO_4$) and concentrated to give 1.84 g of **63**: MS (ESI) m/z 848.0 ($M+H^+$), 869.9 ($M+Na^+$), 886.4 ($M+K^+$), 555.0, 467.0, 295.0; IR (drift) 3288, 1749, 1746, 1686, 1661, 1645, 1642 cm^{-1}.

Step 3:

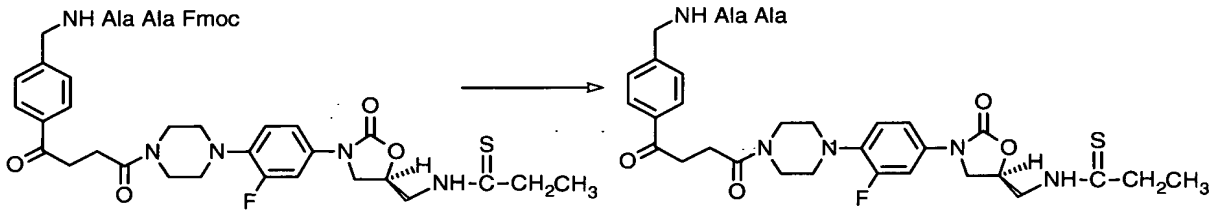


87 **88**

A stirred mixture of **87** (600 mg, 0.708 mmol), triethylamine (236 µL, 1.69 mmol) and MeOH (8 ml) was treated with ethyl dithiopropionate (133 mg, 0.991 mmol) and kept at ambient temperature for 4 d. It was then diluted with CH_2Cl_2 to dissolve the

solids, mixed with silica gel (5 g) and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-CH_2Cl_2 gave 367 mg of **88**, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.13 (t, 3H), 1.22 (q, 6H), 2.57 (q, 2H), 2.72 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.19 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.79 (dd, 1H), 3.90 (t, 2H), 4.17 (m, 6H), 4.33 (d, 2H), 4.94 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.42 (m, 8H), 7.69 (t, 2H), 7.88 (t, 4H), 8.02 (d, 1H), 8.41 (t, 1H), 10.28 (t, 1H).

Step 4:

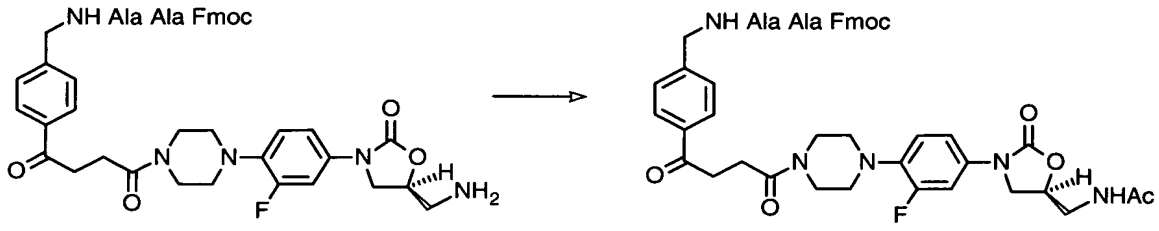


88 **89**

A stirred mixture of **88** (330 mg, 0.359 mmol), trisamine resin (500 mg) and THF (30 ml) was refluxed for 24 h and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel with 7% MeOH-0.7% NH_4OH-$CHCl_3$. Crystallization of the product from MeOH-CH_2Cl_2-heptane gave 151 mg of **89**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.14 (m, 6H), 1.25 (d, 3H), 2.27 (broad s, 2H), 2.58 (q, 2H), 2.74 (t, 2H), 2.92, 3.01 (s, s, 4H), 3.23 (t, 2H), 3.28 (m, 1H), 3.59, 3.68 (s, s, 4H), 3.81 (dd, 1H), 3.92 (t, 2H), 4.14 (t, 1H), 4.35 (m, 3H), 4.95 (m, 1H), 7.09 (t, 1H), 7.18 (dd, 1H), 7.38 (d, 2H), 7.52 (dd, 1H), 7.94 (d, 2H), 8.08 (m, 1H), 8.54 (t, 1H), 10.31 (t, 1H).

Example 27: (*S*)-Alanyl-(*S*)-N^1-(4-{4-[4-(4-{(5*S*)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)alaninamide (91).

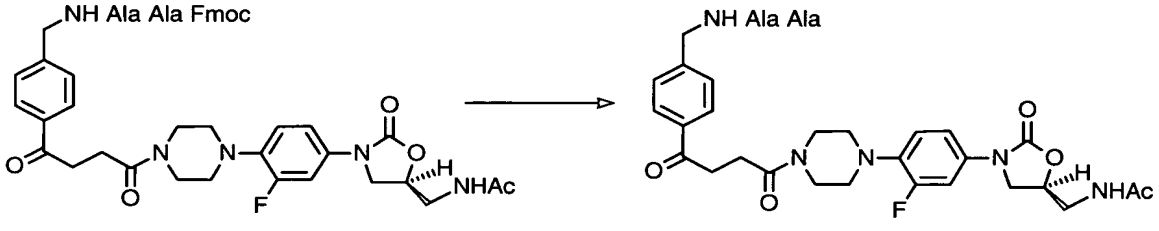
Step 1:



87 90

A stirred mixture of **87** (304 mg, 0.359 mmol) and pyridine (6 ml) was treated with acetic anhydride (51 µL, 0.538 mmol) and kept at ambient temperature for 4 days. It was then concentrated to dryness *in vacuo*. The residue was combined with the product from a similar, 0.118 mmol reaction and 105 mg (0.114 mmol) was removed for a subsequent reaction. The remaining material was chromatographed on silica gel with 10% MeOH-1% NH_4OH-$CHCl_3$ to give 218 mg of **90**: MS (ESI) m/z 890.0 ($M+H^+$), 912.0 ($M+Na^+$), 928.0 ($M+K^+$); IR (drift) 3289, 1744, 1687, 1645 cm^{-1}.

Step 2:

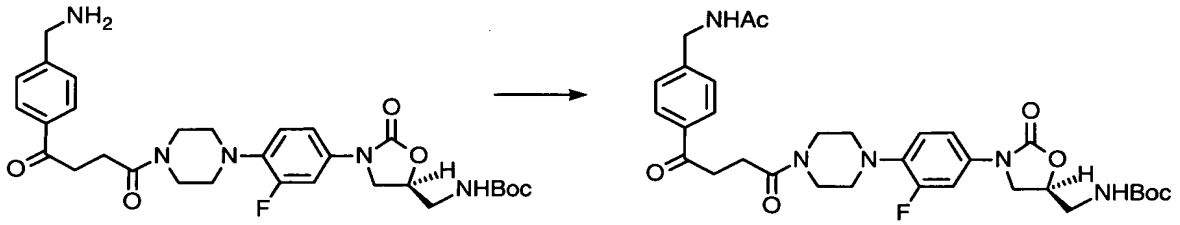


90 91

A stirred mixture of **90** (200 mg, 0.225 mmol) and trisamine resin (550 mg) in THF (25 ml) was refluxed for 4 d, treated with additional resin (250 mg) and refluxed for 1 d. It was then filtered; the filtrate was concentrated and the residue was chromatographed on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$. The product was combined with the product from a similar 0.114 mmol reaction and crystallized from MeOH-CH_2Cl_2-heptane to give 164 mg of **91**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.12 (d, 3H), 1.23 (d, 3H), 1.81 (s, 3H), 2.72 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.21 (t, 2H), 3.31 (m, 1H), 3.38 (t, 2H), 3.62 (m, 5H), 4.08 (t, 1H), 4.33 (m, 3H), 4.68 (m, 1H), 7.07 (t, 1H), 7.15 (d, 1H), 7.35 (d, 2H), 7.48 (d, 1H), 7.92 (d, 2H), 8.05 (s, 1H), 8.23 (t, 1H), 8.52 (t, 1H).

Example 28: N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}benzyl)acetamide (94).

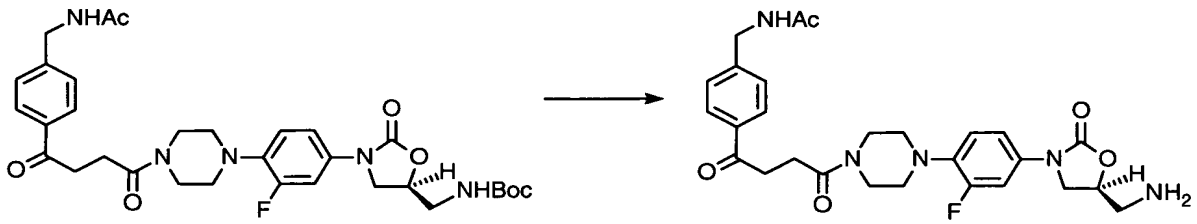
Step 1:



72 92

A stirred solution of **72** (100 mg, 0.171 mmol) in pyridine (2.9 ml) was treated with acetic anhydride (24 μL, 0.257 mmol) and kept at ambient temperature for 1 h. It was then concentrated to dryness *in vacuo*. A solution of the residue in CH_2Cl_2 was treated with heptane to give 100 mg of **92**, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34 (s, 9H), 1.87 (s, 3H), 2.72 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.23 (m, 4H), 3.57, 3.66 (s, s, 4H), 3.74 (dd, 1H), 4.06 (t, 1H), 4.30 (d, 2H), 4.67 (m, 1H), 7.07 (t, 1H), 7.18 (m, 2H), 7.36 (d, 2H), 7.48 (dd, 1H), 7.92 (d, 2H), 8.43 (t, 1H).

Step 2:

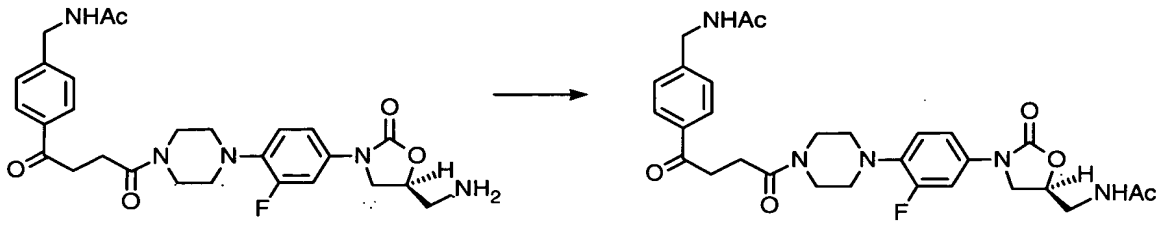


92 93

Solid **92** (2.00 g, 3.20 mmol) was cooled in an ice bath, treated with 4N HCl in dioxane (20 ml) and stirred in the ice bath for 2 h and at ambient temperature for 1 h. It was then concentrated *in vacuo*. A solution of the residue in water (40 ml) was made alkaline with solid $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. A solution of the residue in CH_2Cl_2-MeOH was treated

with heptane and the solid that precipitated was collected by filtration and dried to give 1.45 g of **93**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.87 (s, 3H), 2.06 (broad s, 2H), 2.72 (t, 2H), 2.80 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.21 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.81 (dd, 1H), 4.01 (t, 1H), 4.30 (d, 2H), 4.59 (m, 1H), 7.07 (t, 1H), 7.20 (dd, 1H), 7.36 (d, 2H), 7.51 (dd, 1H), 7.92 (d, 2H), 8.43 (t, 1H).

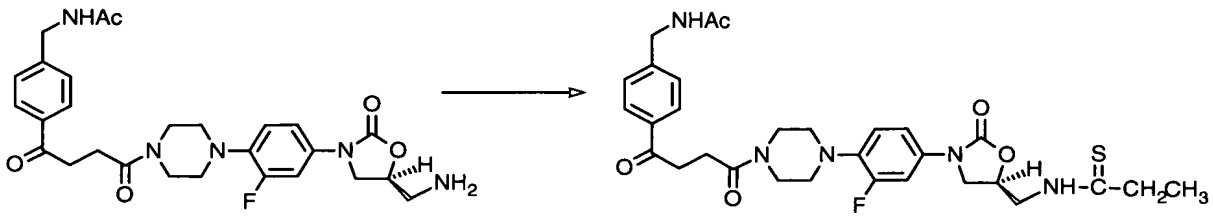
Step 3:



93 **94**

A stirred solution of **93** (500 mg, 0.951 mmol) in pyridine (16 ml) was treated dropwise with acetic anhydride (135 μL, 1.43 mmol), kept at ambient temperature for 4 h and concentrated *in vacuo*. A mixture of the residue and water was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH gave 450 mg of **94**, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 1.87 (s, 3H), 2.72 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.21 (t, 2H), 3.38 (t, 2H), 3.57 (s, 2H), 3.68 (m, 3H), 4.07 (t, 1H), 4.30 (t, 2H), 4.69 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.36 (d, 2H), 7.49 (dd, 1H), 7.92 (d, 2H), 8.23 (t, 1H), 8.43 (t, 1H).

Example 29: N-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethioylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutanoyl}benzyl)acetamide (95).

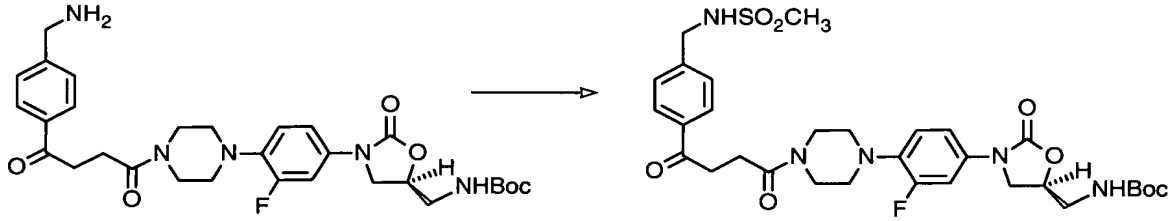


93 95

A stirred solution of **93** (500 mg, 0.951 mmol), triethylamine (662 µL, 4.76 mmol), MeOH (20 ml) and CH_2Cl_2 (10 mL) was treated with ethyl dithiopropionate (384 mg, 2.86 mmol) and kept at ambient temperature for 3 days. It was concentrated *in vacuo*. A solution of the residue in CH_2Cl_2 was washed with 1N HCl and saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The solid residue was triturated with EtOAc-heptane and then crystallized from MeOH to give 466 mg of **95**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.22 (t, 3H), 1.87 (s, 3H), 2.56 (q, 2H), 2.72 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.21 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.79 (dd, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.30 (d, 2H), 4.93 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.36 (d, 2H), 7.49 (dd, 1H), 7.92 (d, 2H), 8.43 (t, 1H), 10.29 (t, 1H).

Example 30: N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-{[(methylsulfonyl)amino]methyl}phenyl)-4-oxobutanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (98).

Step 1:

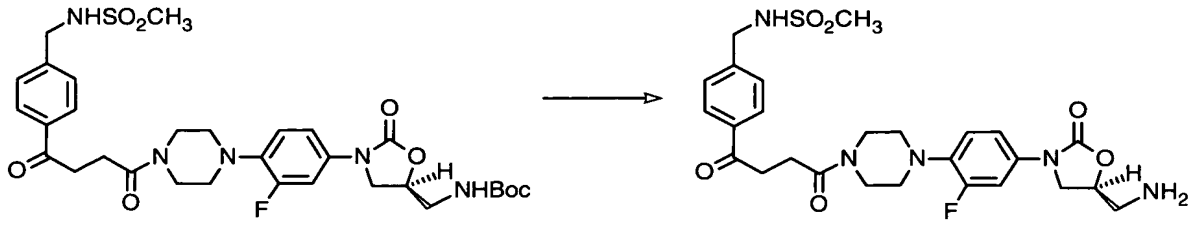


72 96

Methanesulfonyl chloride (432 µL, 3.77 mmol) was added to a stirred solution of **72** (2.00 g, 3.43 mmol) in pyridine (4.0 ml) and the mixture was kept at ambient temperature for 4 h and concentrated *in vacuo*. The residue was mixed with water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. The

residue was triturated with EtOAc to give 2.13 g of **96**: MS (EI) m/z 661.3 (M^+), 308.1; IR (drift) 3360, 3266, 1736, 1684, 1654 cm^{-1}.

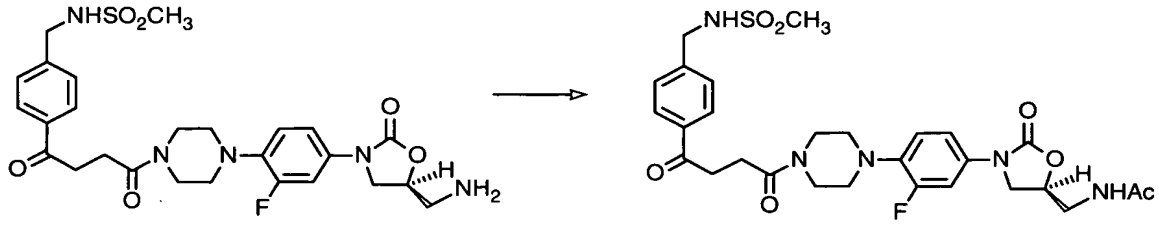
Step 2:



96 **97**

Solid **96** (1.5 g, 2.27 mmol) was cooled, under nitrogen in an ice bath and treated with 4N HCl in dioxane (15 ml). The stirred mixture was kept in the ice bath for 1.5 h and at ambient temperature for 1.5 h and then concentrated *in vacuo*. A solution of the residue in water (25 ml) was made alkaline with $NaHCO_3$ and extracted with 1:5 MeOH:CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH gave 1.00 g of **97**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.72 (broad s), 2.76 (m, 4H), 2.88 (s, 5H), 2.99 (s, 2H), 3.23 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.81 (dd, 1H), 4.01 (t, 1H), 4.23 (s, 2H), 4.57 (m, 1H), 7.07 (t, 1H), 7.19 (dd, 1H), 7.49 (m, 3H), 7.67 (broad s, 1H), 7.96 (d, 2H).

Step 3:

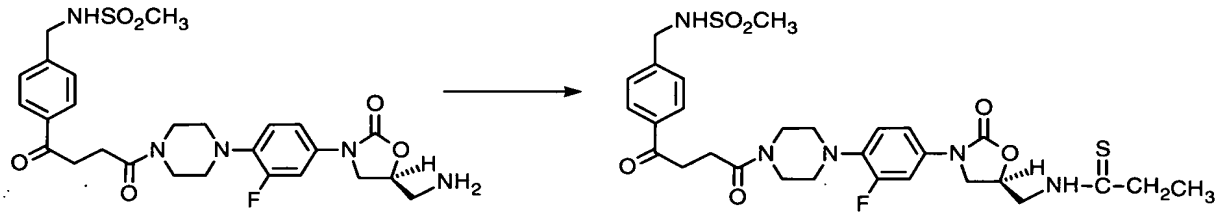


97 **98**

A stirred solution of **97** (500 mg, 0.890 mmol) in pyridine (15 ml) was treated, dropwise with acetic anhydride (126 μL, 1.34 mmol) and kept at ambient temperature for 4 h. It was then concentrated *in vacuo* and the residue was mixed with water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH gave 481 mg of **98**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.83 (s, 3H), 2.75 (t, 2H), 2.90 (s, 5H), 3.02 (s, 2H), 3.25 (t, 2H), 3.40 (t,

2H), 3.60 (s, 2H), 3.68 (m, 3H), 4.09 (t, 1H), 4.25 (d, 2H), 4.71 (m, 1H), 7.09 (t, 1H), 7.18 (dd, 1H), 7.51 (m, 3H), 7.69 (t, 1H), 7.98 (d, 2H), 8.25 (t, 1H).

Example 31: N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-{[(methylsulfonyl)amino]methyl}phenyl)-4-oxobutanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide (99).

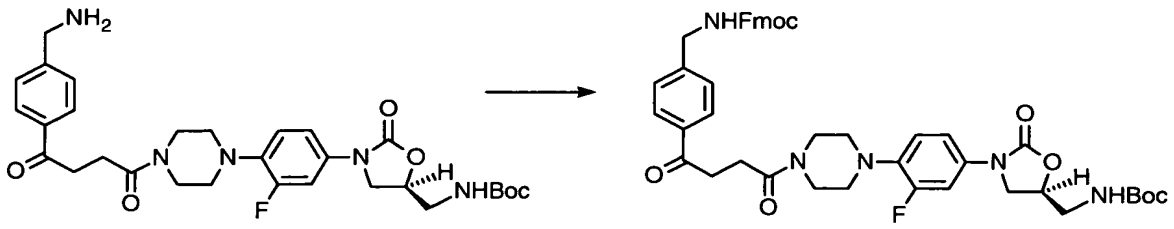


97 99

A stirred mixture of **97** (500 mg, 0.890 mmol), triethylamine (310 µL, 2.23 mmol), ethyl dithiopropionate (179 mg, 1.34 mmol), MeOH (20 ml) and CH_2Cl_2 (15 ml) was kept at ambient temperature for 2 h, treated with additional triethylamine (310 µL) and dithioester (179 mg) and kept at ambient temperature for 3 d. It was then treated with silica gel (5 g) and concentrated. Chromatography of the residue on silica gel with 4% MeOH-CH_2Cl_2 and crystallization of the product from MeOH gave 420 mg of **99**, a white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.15 (t, 3H), 2.59 (q, 2H), 2.75 (t, 2H), 2.90 (s, 3H), 2.91 (s, 2H), 3.02 (s, 2H), 3.25 (t, 2H), 3.60, 3.68, (s, s, 4H), 3.81 (dd, 1H), 3.92 (t, 2H), 4.14 (t, 1H), 4.24 (d, 2H), 4.96 (m, 1H), 7.09 (t, 1H), 7.20 (dd, 1H), 7.51 (m, 3H), 7.69 (t, 1H), 7.98 (d, 2H), 10.32 (t, 1H).

Example 32a: N-({(5*S*)-3-[4-(4-{4-[4-(Aminomethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (103).

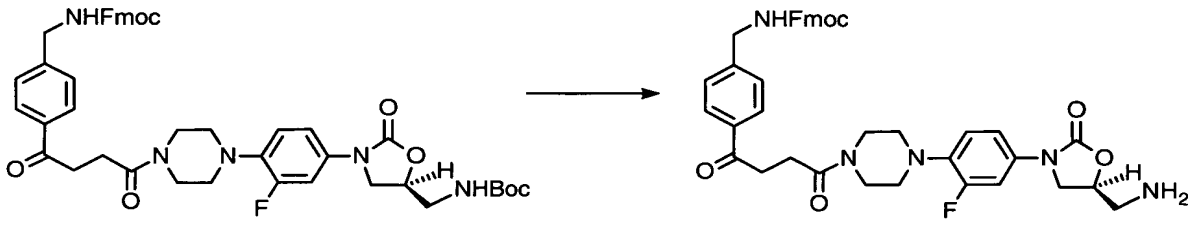
Step 1:



72 100

A stirred, ice cold mixture of **72** (2.46 mmol) and Hunig's base (0.48 ml, 2.71 mmol) in THF (49 ml) was treated with Fmoc-chloride (701 mg, 2.71 mmol) and allowed to warm slowly to ambient temperature and stand for 18 h. It was concentrated, without heating *in vacuo* and the residue was stirred with Et_2O (200 ml) and filtered. The solid was dried to give 2.10 g of **100** as an off-white solid: MS (ESI) m/z 806.1 ($M+H^+$), 827.9 ($M+Na^+$), 844.1 ($M+K^+$); IR (drift) 3353, 1731, 1694, 1685, 1651 cm^{-1}.

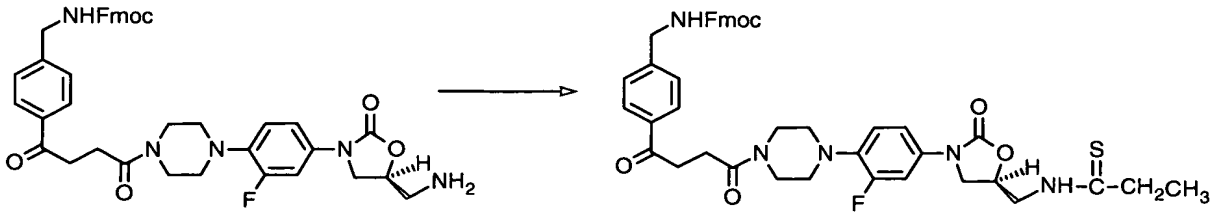
Step 2:



100 101

Ice cold 4N HCl in dioxane (10 ml) was treated with **100** (1.00 g, 1.24 mmol) and the mixture was kept in the ice bath for 1 h and at ambient temperature for 3 h. It was then concentrated *in vacuo*. The residue was mixed with two portions of CH_2Cl_2 (50 ml) with concentration after each addition and the resulting material was mixed with saturated $NaHCO_3$ (20 ml) and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 689 mg of **101**: MS (FAB) m/z 662.3 ($M-CO_2+H^+$), 484.3, 356.1, 355.1, 295.2, 195.1, 179.1; HRMS (FAB) calcd for $C_{39}H_{41}FN_5O_4$ ($M-CO_2+H^+$) 662.3142, found 662.3166; IR (drift) 3288, 1749, 1682, 1645 cm^{-1}.

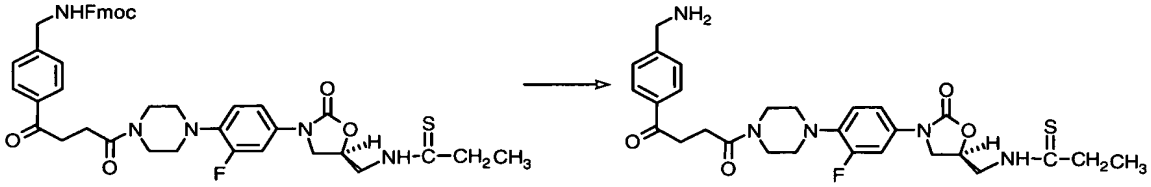
Step 3:



101 102

A stirred mixture of **101** (668 mg, 0.946 mmol), triethylamine (330 µL, 2.37 mmol) and MeOH (10 ml) was treated with ethyl dithiopropionate (152 mg, 1.14 mmol) and CH_2Cl_2 (4 ml) and the resulting solution was kept at ambient temperature for 18 h. It was then mixed with silica gel (2 g) and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc-heptane gave 445 mg of **102**, a white solid: MS (CI) m/z 777.9 (M^+), 619.9; IR (drift) 3306, 1756, 1744, 1692, 1645 cm^{-1}.

Step 4:

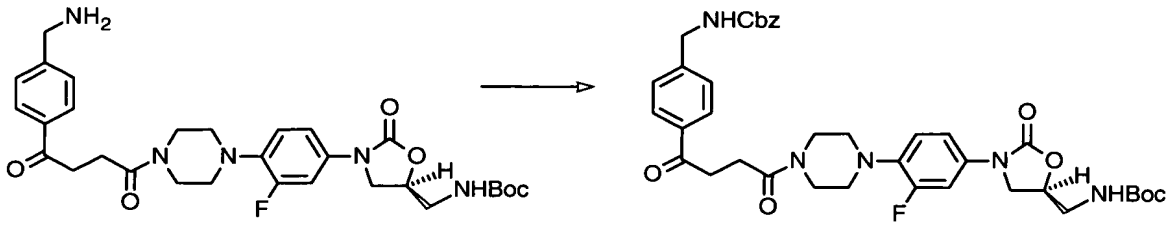


102 103

A stirred solution of **102** (340 mg, 0.437 mmol) in DMF (4.4 ml) was treated with piperidine (108 µL, 1.09 mmol), kept at ambient temperature for 30 min and concentrated *in vacuo*. The residue was chromatographed on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ and the product was crystallized from EtOAc to give 192 mg of **103**, a white solid: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.12 (t, 3H), 2.13 (broad s, 2H), 2.56 (q, 2H), 2.72 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.22 (t, 2H), 3.58, 3.66 (s, s, 4H), 3.77 (m, 3H), 3.90 (s, 2H), 4.11 (t, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.47 (m, 3H), 7.91 (d, 2H), 10.29 (s, 1H).

Example 32b: N-({(5*S*)-3-[4-(4-{4-[4-(Aminomethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (103).

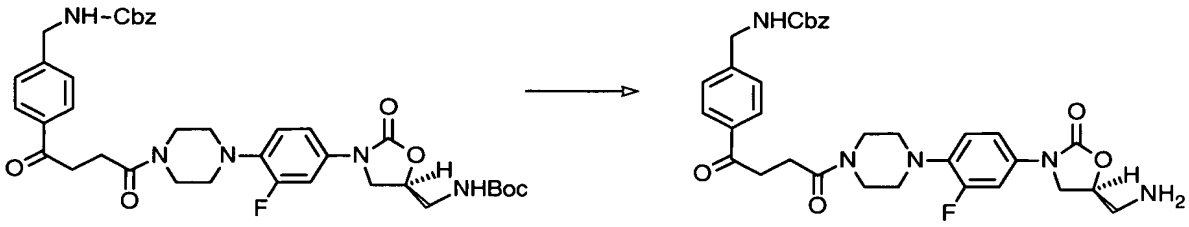
Step 1:



72 104

A stirred, ice cold mixture of **72** (70 mg, 0.12 mmol), $NaHCO_3$ (12 mg, 0.14 mmol) and 3:1 acetone:H_2O (1 ml) was treated with benzyl chloroformate (20 µL, 0.14 mmol) and allowed to warm slowly to ambient temperature and stand for 18 h. It was then mixed with water (15 ml) and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2% MeOH-CH_2Cl_2 and crystallization of the product from EtOAc-heptane gave 51 mg of **104**: mp 158-159°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.82 (t, 2H), 3.01, 3.09 (t, t, 4H), 3.36 (t, 2H), 3.51 (m, 2H), 3.79 (m, 5H), 4.00 (t, 1H), 4.44 (d, 2H), 4.73 (m, 1H), 4.95 (m, 1H), 5.12 (m, 1H), 5.15 (s, 2H), 6.92 (t, 1H), 7.08 (dd, 1H), 7.36 (m, 7H), 7.46 (dd, 1H), 7.98 (d, 2H).

Step 2:

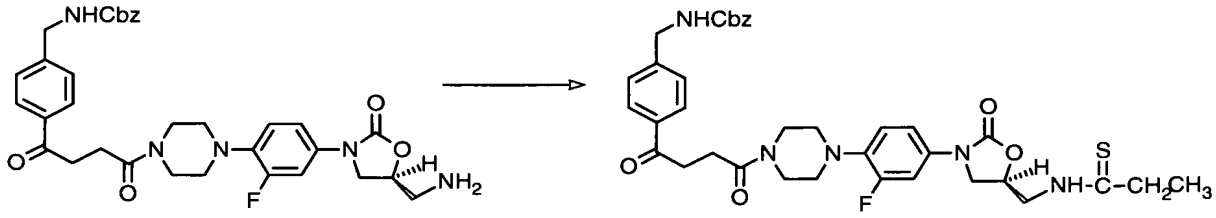


104 105

Solid **103** (830 mg, 1.15 mmol) was cooled in an ice bath and treated with 4N HCl in dioxane (10 ml). The stirred mixture was kept in the ice bath for 1 h and at ambient temperature for 1 h and then concentrated *in vacuo*. The residue was triturated with three portions of CH_2Cl_2 (50 ml) with concentration after each addition. The resulting material was mixed with saturated $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 657 mg of **105**, an off-white

solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (t, 2H), 3.04 (m, 6H), 3.35 (t, 2H), 3.65 (dd, 1H), 3.77 (m, 5H), 4.00 (t, 1H), 4.44 (d, 2H), 4.66 (m, 1H), 5.14 (s, 2H), 5.20 (m, 1H), 6.92 (t, 1H), 7.13 (dd, 1H), 7.36 (m, 7H), 7.49 (dd, 1H), 7.98 (d, 2H).

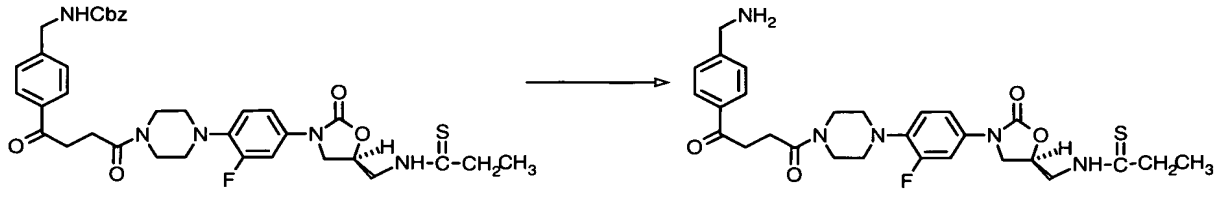
Step 3:



105 106

A stirred mixture of 105 (312 mg, 0.504 mmol), triethylamine (175 μL, 1.26 mmol), ethyl dithiopropionate (74 mg, 0.55 mmol) and MeOH (8 ml) was kept at ambient temperature for 18 h. Methylene chloride (5 ml) and additional dithioester (50 mg) were added and the mixture was kept at ambient temperature for 2 h and concentrated. The residue was stirred for 18 h with a mixture of water (50 ml) and 10% EtOAc-heptane. Chromatography of the resulting solid on silica gel first with 3% MeOH-CH_2Cl_2 and again with 2% MeOH-CH_2Cl_2 and crystallization of the product from EtOAc gave 241 mg of 106: MS (ESI) m/z 690.0 ($M+H^+$), 711.9 ($M+Na^+$), 727.9 ($M+K^+$); IR (drift) 3343, 3202, 1743, 1694, 1646 cm^{-1}.

Step 4:



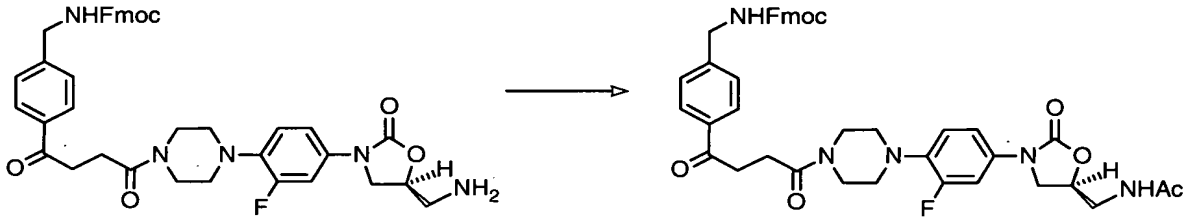
106 103

A stirred mixture of 106 (100 mg, 0.145 mmol) and 30% HBr in HOAc (5 ml) was kept at ambient temperature for 1 h and diluted with Et_2O (60 ml). The resulting solid was collected by filtration and washed with Et_2O. It was then mixed with water (15 ml) and saturated $NaHCO_3$ (15 ml) and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2.5%

MeOH-0.25% NH_4OH-CH_2Cl_2 and crystallization of the product from EtOAc gave 44 mg of **103**, a white solid.

Example 33: N-({(5*S*)-3-[4-(4-{4-[4-(Aminomethyl)phenyl]-4-oxobutanoyl}-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (108).

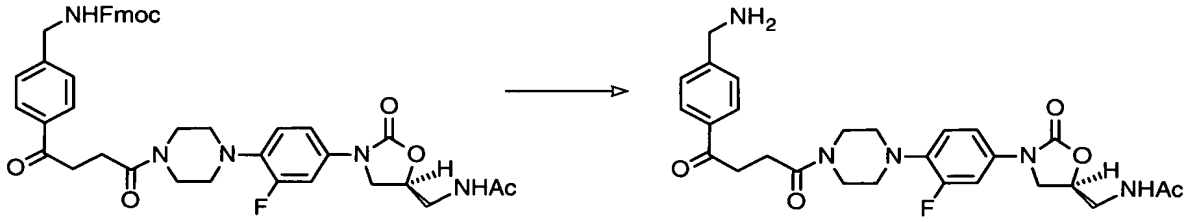
Step 1:



101 **107**

A stirred solution of **101** (755 mg, 1.07 mmol) and triethylamine (1.2 ml, 8.56 mmol) in THF (11 ml) and CH_2Cl_2 (11 ml) was treated with acetyl chloride (139 µL, 1.61 mmol) and kept at ambient temperature for 30 min. It was then mixed with water (30 ml) and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. Trituration of the solid residue with heptane that contained small amounts of acetone, Et_2O, MeOH and EtOAc gave 607 g of **107**, a white solid: MS (ESI) m/z 748.0 ($M+H^+$), 411.9, 231.9; IR (drift) 3305, 1744, 1687, 1646 cm^{-1}.

Step 2:



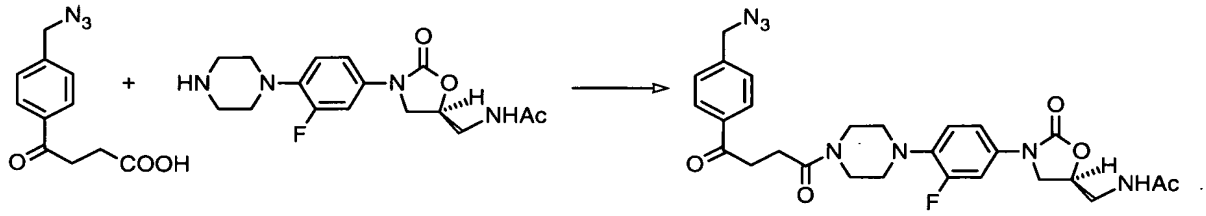
107 **108**

A stirred solution of **107** (576 mg, 0.770 mmol) in DMF (7.8 ml) was treated with piperidine (190 µL, 1.93 mmol), kept at ambient temperature for 30 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ and crystallization of the product from MeOH-CH_2Cl_2-heptane gave a solid that turned yellow when dried at 50°C. It was dissolved in 1:1

CH_2Cl_2:MeOH (50 ml), decolorized with activated carbon and crystallized from CH_2Cl_2-MeOH-Et_2O to give 131 mg of **108**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.72 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.22 (t, 2H), 3.30 (broad s), 3.38 (t, 2H), 3.58 (s, 2H), 3.66 (m, 3H), 3.81 (s, 2H), 4.07 (t, 1H), 4.68 (m, 1H), 7.07 (t, 1H), 7.16 (dd, 1H), 7.49 (m, 3H), 7.92 (d, 2H), 8.23 (t, 1H).

Example 34: N^1-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}benzyl)glycinamide (112).

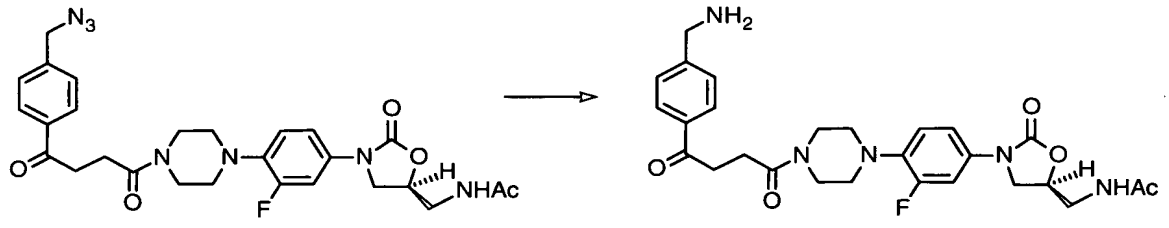
Step 1:



70 **17b** **109**

A stirred, ice cold solution of **70** (1.79 g, 7.67 mmol), **17b** (2.58 g, 7.67 mmol), HOBT (1.14 g, 8.44 mmol) and DMF (67 ml) was treated with EDC (3.23 g, 16.9 mmol) and kept in the ice bath for 2 h and at ambient temperature for 2 h. It was then mixed with water (500 ml) and 1:4 Et_2O:heptane (250 ml). The solid was collected by filtration, dried and chromatographed on silica gel with 5% MeOH-CH_2Cl_2 to give 3.51 g of **109**: MS (EI) m/z 551.2 (M^+), 335.1, 334.1, 307.1; IR (drift) 3307, 2100, 1743, 1688, 1647 cm^{-1}.

Step 2:

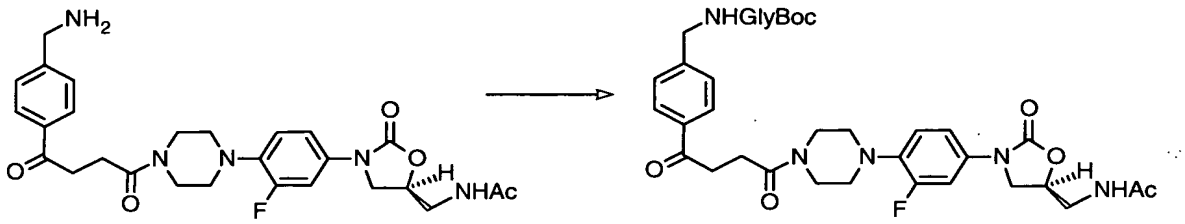


109 **110**

A mixture of **109** (1.50 g, 2.72 mmol), 10% palladium-on-carbon catalyst (375 mg) and THF (90 ml) was hydrogenated for 1 h at an initial pressure of 35 psi. The flask was evacuated and refilled with hydrogen and the reaction was continued for 1 h. Additional catalyst (200 mg) and CH_2Cl_2 (20 ml) were added to the mixture which

was again hydrogenated for 1 h. This mixture was filtered and the filtrate was concentrated. Chromatography of the residue on silica gel with mixtures of MeOH-NH_4OH-CH_2Cl_2 that contained 5-10% MeOH and 0.5-1% NH_4OH gave 876 mg of **110**, a white solid: MS (FAB) m/z 526.3 ($M+H^+$), 337.2, 190.1; IR (drift) 3323, 1743, 1685, 1647 cm^{-1}. Anal. calcd for $C_{27}H_{32}FN_5O_5 \circ 0.5\ H_2O$: C, 60.66; H, 6.22; N, 13.10. Found: C, 60.80; H, 6.22; N, 13.04.

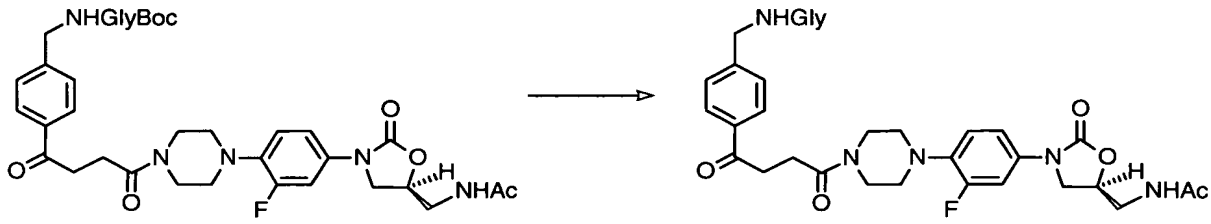
Step 3:



110 **111**

Compound **110** (852 mg, 1.62 mmol) was dissolved in warm DMF (14 ml). The stirred solution was cooled in an ice bath and treated with N-*t*-Boc-glycine (284 mg, 1.62 mmol), HOBT (240 mg, 1.78 mmol) and finally EDC (682 mg, 3.56 mmol). It was kept in the ice bath for 2 h and at ambient temperature for 2 h and then mixed with water (150 ml). The resulting solid was collected by filtration, washed with water and then with 1:1 Et_2O-heptane and dried to give 998 mg of **111**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.37 (s, 9H), 1.81 (s, 3H), 2.72 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.21 (t, 2H), 3.38 (t, 2H), 3.56 (m, 4H), 3.66 (m, 3H), 4.07 (t, 1H), 4.33 (d, 2H), 4.69 (m, 1H), 7.07 (m, 2H), 7.16 (dd, 1H), 7.37 (d, 2H), 7.49 (dd, 1H), 7.90 (d, 2H), 8.23 (t, 1H), 8.38 (t, 1H).

Step 4:

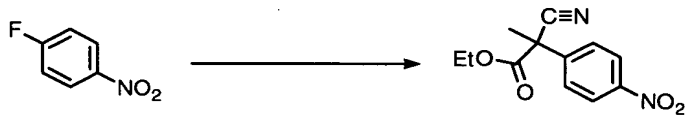


111 **112**

Solid **111** (830 mg, 1.22 mmol) was cooled in an ice bath under nitrogen, and treated with 4N HCl in dioxane (10 ml). The mixture was stirred in the ice bath for 1.5 h and then concentrated *in vacuo*. A solution of the residue in water (15 ml) was made alkaline with solid $NaHCO_3$ and freeze dried. The resulting solid was extracted with MeOH-CH_2Cl_2 and the extract was concentrated. Chromatography of the residue on silica gel with 10-20% MeOH-CH_2Cl_2 and crystallization of the product from MeOH-CH_2Cl_2-heptane gave 338 mg of **112**, as an off-white solid: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.72 (t, 2H), 2.72 (broad s, 2H), 2.89, 2.99 (s, s, 4H), 3.18 (s, 2H), 3.21 (t, 2H), 3.38 (t, 2H), 3.57 (s, 2H), 3.68 (m, 3H), 4.07 (t, 1H), 4.35 (d, 2H), 4.69 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.38 (d, 2H), 7.49 (dd, 1H), 7.92 (d, 2H), 8.24 (t, 1H), 8.46 (t, 1H).

EXAMPLE 35: 2-[3-methyl-3-(4-{(5S)-2-oxo-5-[(propionylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)azetidin-1-yl]-2-oxoethyl 4-(aminomethyl)benzamide (120).

Step 1:

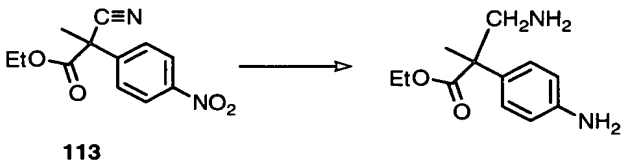


113

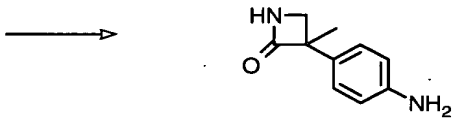
A suspension of anhydrous K_2CO_3 (13.0 g, 94.3 mmol) in CH_3CN (175 mL) is treated with ethyl cyanoacetate (5.0 mL, 47.1 mmol) at rt with stirring. The reaction is warmed to 75 °C for 20 min, then cooled to 0 °C with an ice bath followed by dropwise treatment with 1-fluoro-4-nitrobenzene (5.0 mL, 47.1 mmol) over 5 min. The ice bath is removed and the red suspension is warmed to 75 °C for 18 h. The dark red suspension is then cooled to rt, treated with iodomethane (26.4 mL, 424.2 mmol), K_2CO_3 (19.5 g, 141.4 mmol), acetone (60 mL), and then warmed to 60 °C for 24 h. The pink suspension is then cooled to rt and filtered through Celite (repeated EtOAc washings). After concentrating the filtrate *in vacuo*, the orange-brown residue is diluted with H_2O (300 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts are washed with brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product via Biotage chromatography (eluting with 20% EtOAc/Hexane) affords **113** (4.87 g) as a white solid. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.27 (d, J = 8.9 Hz, 2 H), 7.73 (d, J = 9.1 Hz, 2 H), 4.26 (m, 2 H), 1.99 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H).

Step 2:



113

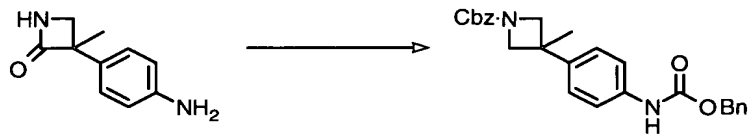


114

A solution **113** (15.8 g, 63.8 mmol) in absolute EtOH (650 mL) is treated with Raney nickel (34.5 g of a 50% slurry in H_2O) and subjected to hydrogenation in a Parr apparatus for 18 h (25-30 psi H_2, rt). The reaction mixture is then filtered through Celite (repeated EtOH washings) and concentrated *in vacuo*. Purification of the crude product via Biotage chromatography (eluting with 15% MeOH/EtOAc) affords the reduced amino-aniline compound corresponding to **113** (11.36 g) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.7 Hz, 2 H), 6.63 (d, J = 8.7 Hz, 2 H), 4.13 (m, 2 H), 3.09 (d, J = 13.3 Hz, 1 H), 2.94 (d, J = 13.5 Hz, 1 H), 1.52 (s, 3 H), 1.19 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.87, 145.17, 131.43, 127.06, 115.02, 60.61, 51.74, 51.14, 20.81, 14.05. A solution of this amino-aniline (8.3 g, 37.3 mmol) in THF (207 mL) is added dropwise to a 0 °C solution of methyl magnesium bromide (62.2 mL, 3.0 M in Et_2O) in THF (415 mL). When addition is complete, THF (30 mL) is used to rinse the addition funnel, and then the ice bath is removed and reaction stirred at rt for 3 h. The reaction contents are poured into saturated aqueous NH_4Cl (1000 mL) and volatiles are removed *in vacuo*. The aqueous phase is extracted with $CHCl_3$ (4 x 300 mL). The combined organic extracts are washed with H_2O (200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product via Biotage chromatography (eluting with 50% EtOAc/hexane) affords **114** (4.65 g) as an off-white solid in 71% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 2 H), 6.65 (d, J = 8.3 Hz, 2 H), 6.13 (s, 1 H), 3.48 (d, J = 5.3 Hz, 1 H), 3.36 (d, J = 5.3 Hz, 1 H), 1.62 (s, 3 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 173.44, 145.30, 130.60, 126.71, 115.15, 59.41, 51.40, 23.14; MS (ESI+) for $C_{10}H_{12}N_2O$ *m/z* 177.1 $(M+H)^+$.

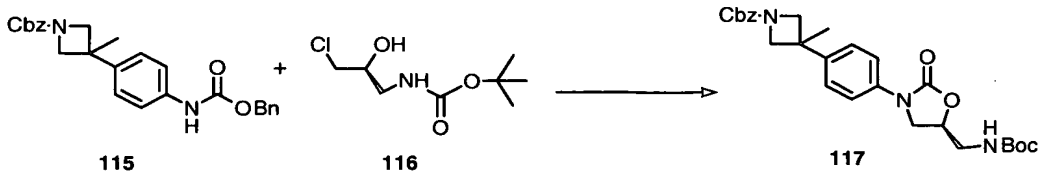
Step 3:



114 115

A solution of $LiAlH_4$ (79.2 mL, 1.0 M in THF) is diluted with THF (77 mL) and cooled to 0 °C. To this is added a solution of 114 (4.65 g, 26.4 mmol) in THF (116 mL), with gas evolution. The ice bath is removed and the reaction was heated to reflux (75 °C oil bath) for 22 h, during which time the reaction became a white suspension. After cooling to rt, the mixture was treated successively with H_2O (3.01 mL), 5 N aqueous NaOH (2.71 mL), and H_2O (10.52 mL). The resulting suspension was diluted with EtOAc (600 mL), filtered through a pad of Celite, rinsing the Celite with additional EtOAc (400 mL). Concentration *in vacuo* affords the desired azetidine (4.76 g) as a yellow oil. A solution of this crude intermediate in acetone (85 mL) and H_2O (47 mL) was treated with sodium bicarbonate (19.96 g, 237.6 mmol). The resulting suspension was cooled to 0 °C and treated with benzylchloroformate (18.84 mL, 132.0 mmol) with gas evolution. The ice bath was removed and the reaction mixture was stirred overnight at rt. In the a.m., the reaction mixture was diluted with saturated aqueous sodium bicarbonate (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product via Biotage chromatography (eluting with 25% EtOAc/hexane) affords (4.75 g) as a pale yellow syrup; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 12 H), 7.13 (d, J = 8.7 Hz, 2 H), 6.77 (s, 1 H), 5.19 (s, 2 H), 5.10 (s, 2 H), 4.22 (d, J = 8.3 Hz, 2 H), 3.97 (d, J = 8.3 Hz, 2 H), 1.59 (s, 3 H); MS (ESI-) for $C_{26}H_{26}N_2O_4$ *m/z* 429.0 $(M-H)^-$.

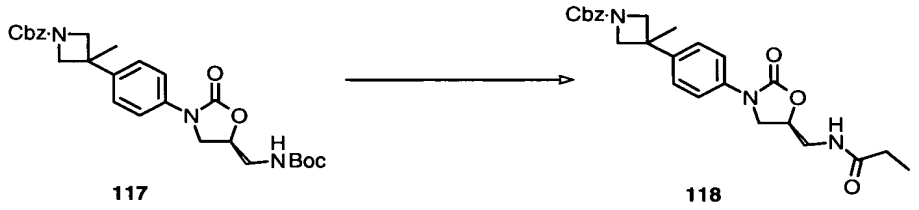
Step 4:



115 116 117

A solution of 116 (4.75 g, 11.03 mmol) in DMF (20 mL) at 0 °C is treated with LiO*t*-Bu (33.1 mL, 1.0 M solution in hexanes) dropwise over 25 min. After an additional 20 min, the reaction is treated with 116 (4.63 g, 22.07 mmol, U.S. Patent Publication Application 2002/0086900) and stirred 14h with ice bath expiring. The reaction is quenched with saturated aqueous NH_4Cl (85 mL) and then extracted with EtOAc (3 x 80 mL). The combined organic extracts are washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product via Biotage chromatography (eluting with 50% EtOAc/hexane) affords 117 (4.16 g) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.7 Hz, 2 H), 7.39-7.30 (m, 5 H), 7.31 (d, J = 8.7 Hz, 2 H), 7.22 (t, J = 5.9 Hz, 1 H), 5.05 (s, 2 H), 4.68 (m, 1 H), 4.14 (m, 2 H), 4.10 (t, J = 9.0 Hz, 1 H), 3.95 (m, 2 H), 3.78 (dd, J = 9.0, 5.9 Hz, 1 H), 3.27 (t, J = 5.4 Hz, 2 H), 1.54 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.86, 154.03, 141.54, 136.73, 136.56, 128.28, 127.75, 127.52, 125.73, 117.96, 77.96, 71.28, 65.62, 47.03, 42.79, 37.69, 28.79, 28.00.

Step 5:

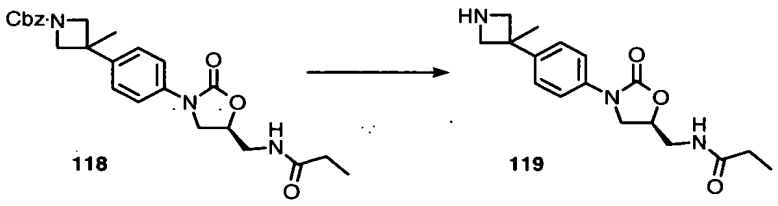


117 118

A solution of 117 (4.10 g, 8.37 mmol) in MeOH (20 mL) at 0 °C is treated with 4 M HCl-dioxane (5.0 mL) and stirred for 10 min. The ice bath is then removed, and after stirring 20 h at rt, the solution is concentrated *in vacuo*. The resulting pale yellow solid is subsequently treated with pyridine (12 mL) and propionic anhydride (6 mL) in CH_2Cl_2 (30 mL) at 0 °C and stirred 14h with bath expiring. The reaction is quenched with H_2O (150 mL), and the layers are separated. The organic layer is washed with 1.0 M HCl (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*.

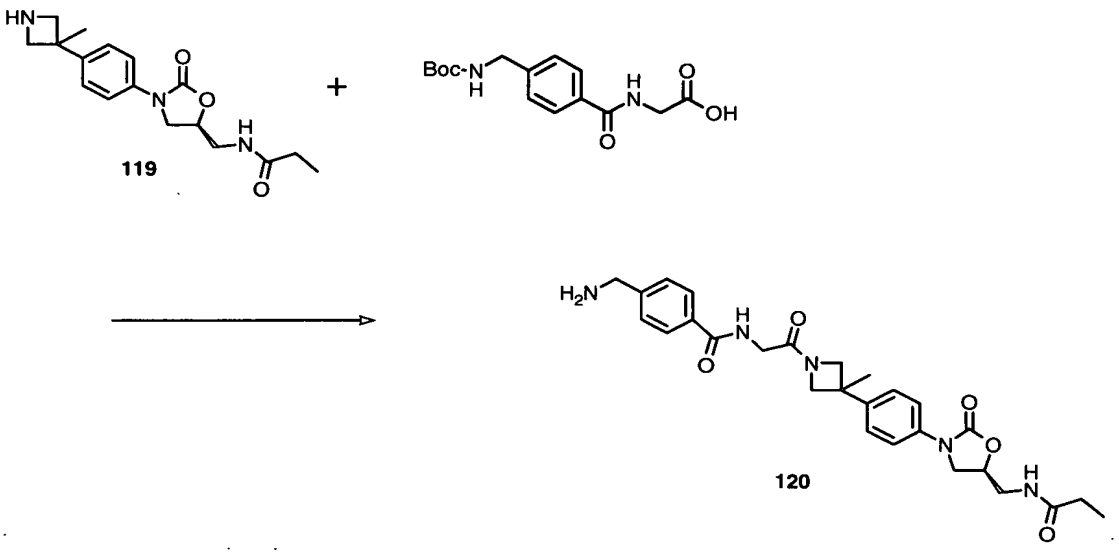
Trituration (Et_2O) affords (2.98 g) as a white solid in 79% yield; ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (t, J = 5.8 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 2 H), 7.39-7.30 (m, 5 H), 7.31 (d, J = 8.5 Hz, 2 H), 5.05 (s, 2 H), 4.72 (m, 1 H), 4.13 (m, 2 H), 4.11 (t, J = 8.9 Hz, 1 H), 3.96 (m, 2 H), 3.74 (dd, J = 8.9, 6.2 Hz, 1 H), 3.42 (m, 2 H), 2.10 (q, J = 7.7 Hz, 2 H), 1.54 (s, 3 H), 0.96 (t, J = 7.7 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.65, 155.88, 154.04, 141.56, 136.74, 136.52, 128.29, 127.75, 127.53, 125.75, 117.98, 71.43, 65.64, 47.11, 41.24, 37.69, 28.78, 28.25, 9.81.

Step 6:



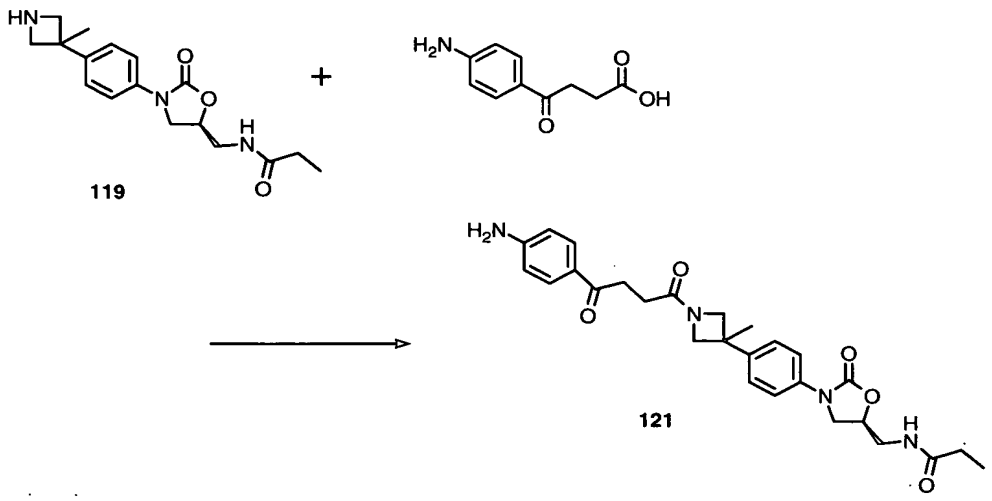
A solution of **118** (2.78 g, 6.16 mmol) in 5:1 MeOH:THF (60 mL) was placed under N_2 (g) and then treated with 10% Pd/C (278 mg). The reaction vessel was then charged with H_2 (g) and the reaction mixture was stirred overnight at rt. In the a.m., the mixture was filtered and concentrated *in vacuo*. Purification of the crude product via Biotage chromatography (eluting first with 10% MeOH/CH_2Cl_2 and then with 5-15% MeOH(NH_3)/CH_2Cl_2) affords (1.79 g) as a white solid; ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (t, J = 5.8 Hz, 1 H), 7.47 (d, J = 8.9 Hz, 2 H), 7.21 (d, J = 8.7 Hz, 2 H), 4.71 (m, 1 H), 4.10 (t, J = 9.0 Hz, 1 H), 3.74 (t, J = 6.4 Hz, 1 H), 3.73 (d, J = 6.6 Hz, 2 H), 3.42 (m, 2 H), 3.38 (d, J = 7.5 Hz, 2 H), 2.10 (q, J = 7.5 Hz, 2 H), 1.53 (s, 3 H), 0.96 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.65, 154.06, 144.21, 135.92, 125.29, 117.95, 71.39, 58.27, 47.15, 41.91, 41.25, 28.64, 28.25, 9.82 1.41.

Step 7:



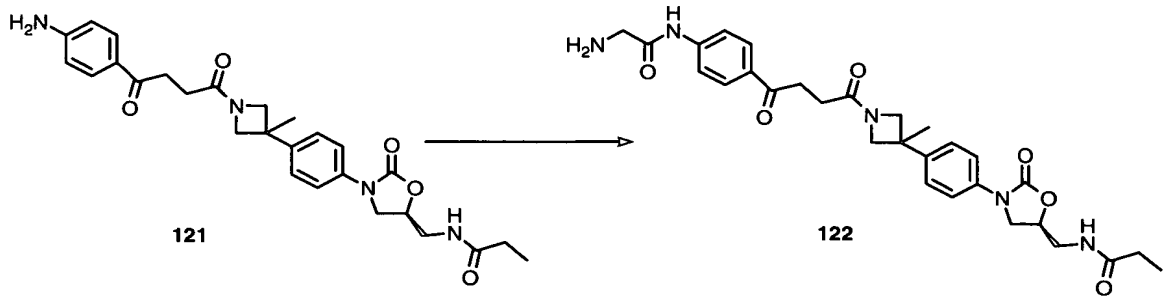
A solution of **119** (241 mg, 0.76 mmol) and N-(4-{[(tert-butoxycarbonyl)-amino]methyl}benzoyl)glycine (246 mg, 0.80 mmol) in CH_3CN (20 mL) at 0 °C was treated with HATU (304 mg, 0.80 mmol) followed by Hunig's base (0.70 mL, 3.99 mmol) and stirred overnight with ice bath expiring. In the a.m., the reaction mixture was concentrated *in vacuo*, and the residue dissolved in CH_2Cl_2 (200 mL). This organic phase was washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow-brown solid. Purification via Biotage chromatography (eluting with 2-10% MeOH/CH_2Cl_2) affords the Boc-protected amine (352 mg) as a glassy film in 76% yield. This compound (300 mg) was subsequently treated with TFA (2.0 mL) in CH_2Cl_2 (7.0 mL) at 0 °C for 10 min, and then stirred an additional 2h at rt. Concentration *in vacuo* followed by purification via Biotage chromatography (eluting first with 10% MeOH/CH_2Cl_2 and then with 10% MeOH(NH_3)/CH_2Cl_2) affords **120** (217 mg) as a pale yellow; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (t, J = 5.7 Hz, 1 H), 8.19 (t, J = 5.9 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 7.53 (d, J = 8.9 Hz, 2 H), 7.44 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.7 Hz, 2 H), 4.73 (m, 1 H), 4.45 (d, J = 8.3 Hz, 1 H), 4.25 (d, J = 8.3 Hz, 1 H), 4.12 (t, J = 9.1 Hz, 1 H), 4.09 (d, J = 9.1 Hz, 1 H), 3.90 (m, 3 H), 3.82 (s, 2 H), 3.76 (dd, J = 9.0, 6.3 Hz, 1 H), 3.42 (m, 4 H), 2.10 (q, J = 7.7 Hz, 2 H), 1.57 (s, 3 H), 0.96 (t, J = 7.6 Hz, 3 H).

Example 36: N-{[(5S)-3-(4-{1-[4-(4-aminophenyl)-4-oxobutanoyl]-3-methylazetidin-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanamide (121).



A mixture of **119** (1.50 g, 4.73 mmol), 4-(4-aminophenyl)-4-oxobutanoic acid (1.10 g, 5.67 mmol), HOBt (703 mg, 5.20 mmol), and Hunig's base (2.06 mL, 11.83 mmol) in CH_2Cl_2 (25 mL) at 0 °C was treated with EDCI (1.99 g, 10.40 mmol) and stirred 14h with ice bath expiring. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL) and layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a black foamy solid. Purification via Biotage chromatography (eluting with 2% $MeOH(NH_3)/CH_2Cl_2$) gave **121** (1.76 g) as a pale red solid in 76% yield; ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (t, J = 5.5 Hz, 1 H), 7.68 (d, J = 8.7 Hz, 2 H), 7.52 (d, J = 8.7 Hz, 2 H), 7.34 (d, J = 8.7 Hz, 2 H), 6.56 (d, J = 8.7 Hz, 2 H), 6.02 (s, 2 H), 4.72 (m, 1 H), 4.41 (d, J = 7.9 Hz, 1 H), 4.20 (d, J = 7.9 Hz, 1 H), 4.12 (t, J = 9.0 Hz, 1 H), 4.01 (d, J = 9.0 Hz, 1 H), 3.85 (d, J = 9.0 Hz, 1 H), 3.76 (dd, J = 9.0, 6.4 Hz, 1 H), 3.42 (m, 2 H), 3.07 (t, J = 6.4 Hz, 2 H), 2.37 (t, J = 6.0 Hz, 2 H), 2.10 (q, J = 7.7 Hz, 2 H), 1.57 (s, 3 H), 0.96 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.57, 173.66, 172.10, 154.05, 153.47, 141.73, 136.51, 130.09, 125.84, 124.18, 117.99, 112.34, 71.43, 61.85, 59.78, 47.12, 41.25, 37.01, 31.77, 28.84, 28.26, 24.84, 9.83.

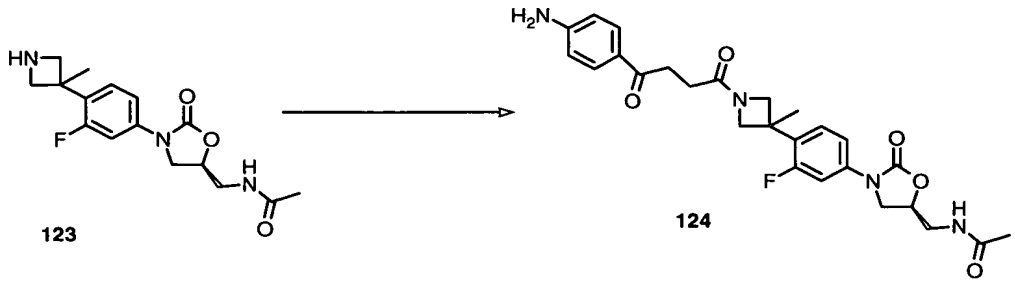
Example 37: N-({(5S)-3-[4-(1-{4-[4-(glycylamino)phenyl]-4-oxobutanoyl}-3-methylazetidin-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide (122).



121 122

A solution of **121** (from Example 36)(1.00 g, 2.03 mmol) and FmocGlyCl (770 mg, 2.44 mmol) in CH_2Cl_2 (15 mL) at rt was treated with pyridine (0.82 mL, 10.15 mmol) and let stir for 90 min. The reaction was then diluted with CH_2Cl_2 (200 mL), washed with H_2O (75 mL), 0.1 M HCl (75 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a light brown foamy solid. Purification via Biotage chromatography (eluting with 5% MeOH/CH_2Cl_2) affords the Fmoc-protected derivative of glycyl-amine **122** (598 mg) as a pale brown solid. This compound was subsequently treated with piperidine (0.19 mL) in DMF (5.0 mL) at rt for 20 min, and then concentrated *in vacuo*. Purification via Biotage chromatography (eluting first with 5-10% MeOH/CH_2Cl_2 and then with 10% MeOH(NH_3)/CH_2Cl_2) followed by trituration (Et_2O) affords **122** (258 mg) as a pale grey solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (t, J = 5.7 Hz, 1 H), 7.95 (d, J = 8.7 Hz, 2 H), 7.78 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H), 7.35 (d, J = 8.7 Hz, 2 H), 4.73 (m, 1 H), 4.42 (d, J = 8.1 Hz, 1 H), 4.22 (d, J = 8.1 Hz, 1 H), 4.13 (t, J = 9.1 Hz, 1 H), 4.03 (d, J = 9.1 Hz, 1 H), 3.86 (d, J = 9.3 Hz, 1 H), 3.76 (dd, J = 9.0, 6.3 Hz, 1 H), 3.43 (m, 3 H), 3.31 (s, 2 H), 3.21 (t, J = 6.2 Hz, 2 H), 2.43 (t, J = 5.6 Hz, 2 H), 2.11 (q, J = 7.7 Hz, 2 H), 1.58 (s, 3 H), 0.96 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.19, 173.67, 172.62, 171.81, 154.06, 143.01, 141.70, 136.53, 131.11, 129.07, 125.84, 118.13, 117.99, 71.45, 61.84, 59.80, 54.81, 47.12, 45.55, 41.25, 37.07, 32.43, 28.86, 28.26, 24.69, 9.83.

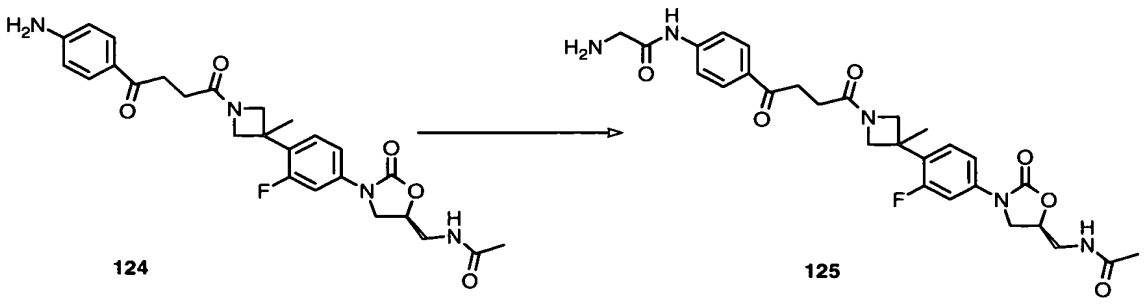
Example 38: N-{[(5S)-3-(4-{1-[4-(4-aminophenyl)-4-oxobutanoyl]-3-methylazetidin-3-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (124).



123 124

A solution of **123** (Prepared as described in U.S. Patent No. 5,968,962, 1.50 g, 3.34 mmol), 4-(4-aminophenyl)-4-oxobutanoic acid (645 mg, 3.34 mmol), and Hunig's base (2.91 mL, 16.69 mmol) in CH_3CN (56 mL) at 0 °C was treated dropwise with a solution of HATU (1.33 g, 3.51 mmol) in CH_3CN (38 mL). Additional Hunig's base (2.91 mL) was added to obtain full dissolution of starting material, and the reaction was stirred 14h with ice bath expiring. The reaction mixture was concentrated *in vacuo*, and residue was dissolved in CH_2Cl_2. This organic layer was washed initially with 1.0 M HCl; however, back-extraction with CH_2Cl_2 was necessary to retrieve much of the desired product from the aqueous layer. The organic layers are combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification via Biotage chromatography (eluting with 4% MeOH/CH_2Cl_2) affords **124** (1.42 g) as a red solid in 86% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (t, J = 5.8 Hz, 1 H), 7.67 (d, J = 8.5 Hz, 2 H), 7.50 (dd, J = 13.5, 1.7 Hz, 1 H), 7.31 (m, 2 H), 6.55 (d, J = 8.7 Hz, 2 H), 6.02 (s, 2 H), 4.74 (m, 1 H), 4.48 (d, J = 8.1 Hz, 1 H), 4.21 (d, J = 8.3 Hz, 1 H), 4.12 (m, 2 H), 3.85 (d, J = 9.3 Hz, 1 H), 3.74 (dd, J = 9.1, 6.4 Hz, 1 H), 3.42 (t, J = 5.5 Hz, 2 H), 3.06 (t, J = 6.4 Hz, 2 H), 2.36 (m, 2 H), 1.84 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.52, 172.19, 169.88, 161.26, 158.05, 153.88, 153.46, 138.57, 138.43, 130.07, 127.82, 127.74, 127.63, 127.43, 124.15, 113.41, 112.32, 105.66, 105.30, 71.58, 60.77, 58.62, 54.81, 47.07, 41.25, 35.07, 31.73, 28.02, 24.84, 22.34.

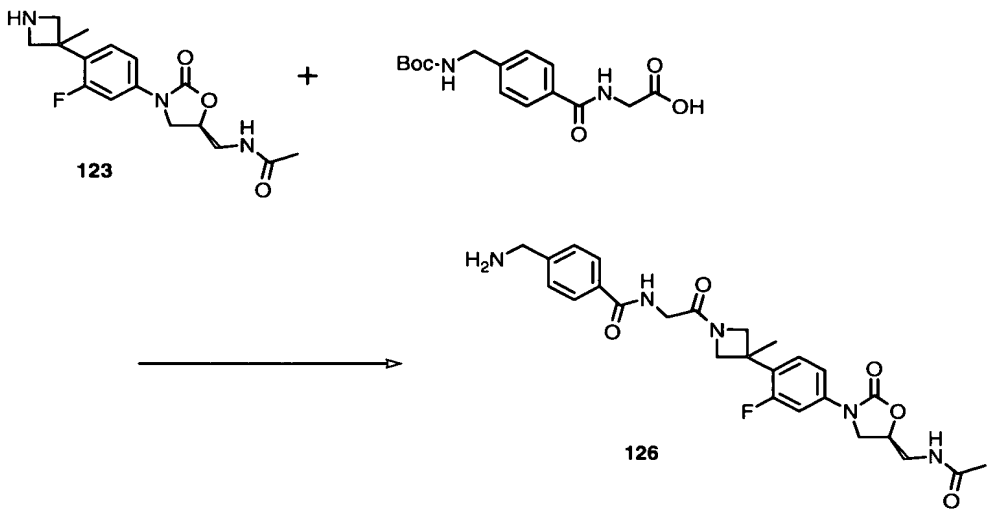
Example 39: N~1~-(4-{4-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-methylazetidin-1-yl]-4-oxobutanoyl}phenyl)glycinamide (125).



124 125

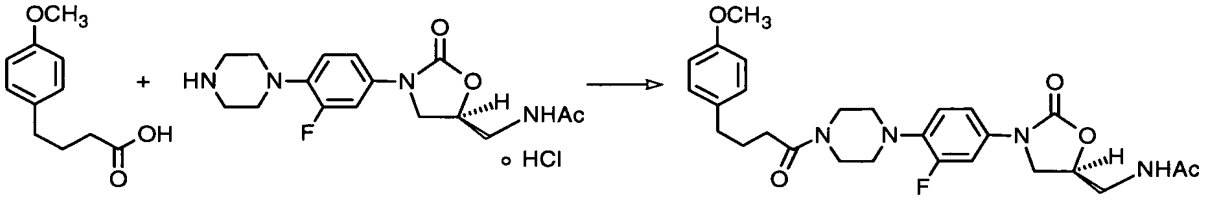
A solution of **124** (from Example 38) (790 mg, 1.59 mmol) and CbzGlyOH (349 mg, 1.67 mmol) in CH_3CN (40 mL) at 0 °C was treated with Hunig's base (1.39 mL, 7.96 mmol) followed by HATU (635 mg, 1.67 mmol) and stirred 14h with ice bath expiring. The reaction mixture was concentrated *in vacuo*, and the residue dissolved in CH_2Cl_2 (200 mL). This organic phase was washed with 1.0 M HCl, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification via Biotage chromatography (eluting with 5% $MeOH/CH_2Cl_2$) affords the Cbz-protected amine (313 mg) as a pale yellow solid in 29% yield. This compound was subsequently placed under N_2 (g) in 10:1 THF:MeOH (11 mL) and treated with Pd/C (80 mg). The reaction vessel was then charged with H_2 (g) and the reaction mixture was stirred for 2 d at rt. After filtering to remove Pd/C, the filtrate was concentrated *in vacuo*. Purification via Biotage chromatography (eluting with 4% $MeOH(NH_3)/CH_2Cl_2$) affords **125** (99 mg) as a pale yellow-green solid: ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 (t, J = 5.8 Hz, 1 H), 7.94 (d, J = 8.9 Hz, 2 H), 7.77 (d, J = 8.7 Hz, 2 H), 7.50 (dd, J = 13.6, 1.6 Hz, 1 H), 7.31 (m, 2 H), 4.74 (m, 1 H), 4.49 (d, J = 8.1 Hz, 1 H), 4.22 (d, J = 8.1 Hz, 1 H), 4.13 (m, 2 H), 3.86 (d, J = 9.3 Hz, 1 H), 3.74 (dd, J = 9.0, 6.5 Hz, 1 H), 3.42 (t, J = 5.4 Hz, 2 H), 3.32 (s, 2 H), 3.20 (t, J = 6.3 Hz, 2 H), 2.42 (m, 2 H), 1.84 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.15, 172.49, 171.89, 169.89, 161.28, 158.06, 153.89, 142.99, 138.59, 138.45, 131.11, 129.07, 127.83, 127.71, 127.60, 127.42, 118.13, 113.42, 105.67, 105.31, 71.59, 60.81, 58.69, 48.48, 47.08, 45.47, 41.26, 35.14, 32.41, 28.03, 24.71, 22.34.

Example 40: Preparation of 2-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-methylazetidin-1-yl]-2-oxoethyl-4-(aminomethyl)benzamide (126).



A solution of N-(4-{[(tert-butoxycarbonyl)amino]methyl}benzoyl)glycine (216 mg, 0.70 mmol) and Hunig's base (0.23 mL, 1.34 mmol) in CH_3CN (10 mL) at 0 °C was treated with HATU (266 mg, 0.70 mmol) and let stir for 35 min. A solution of **123** (300 mg, 0.67 mmol) in CH_3CN/DMF (5 mL/1 mL) was added along with more Hunig's base (0.35 mL, 2.00 mmol). The reaction was stirred for 30 min with ice bath expiring, then concentrated *in vacuo*, and the amber residue was dissolved in CH_2Cl_2 (100 mL), washed with 0.1 M HCl (2 x 30 mL), saturated aqueous $NaHCO_3$ (40 mL), brine (40 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow-brown solid. Purification via Biotage chromatography (eluting with 4-5% MeOH/CH_2Cl_2) affords the Boc-protected amine (300 mg) as a white solid in 74% yield. This compound (750 mg) was treated with TFA (3.0 mL) in CH_2Cl_2 (10 mL) at 0 °C for 20 min, and then stirred an additional 50 min at rt. Concentration *in vacuo* followed by purification via Biotage chromatography (eluting first with 5% MeOH/CH_2Cl_2 and then with 5% MeOH(NH_3)/CH_2Cl_2) and trituration (Et_2O) affords **126** (463 mg) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (t, J = 5.6 Hz, 1 H), 8.26 (t, J = 5.8 Hz, 1 H), 7.81 (d, J = 8.1 Hz, 2 H), 7.51 (dd, J = 13.7, 1.9 Hz, 1 H), 7.42 (d, J = 8.3 Hz, 2 H), 7.31 (m, 2 H), 4.74 (m, 1 H), 4.52 (d, J = 8.3 Hz, 1 H), 4.26 (d, J = 8.5 Hz, 1 H), 4.18 (d, J = 9.5 Hz, 1 H), 4.12 (t, J = 9.0 Hz, 1 H), 3.88 (m, 3 H), 3.76 (s, 2 H), 3.74 (dd, J = 9.0, 6.4 Hz, 1 H), 3.42 (t, J = 5.4 Hz, 2 H), 1.84 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.89, 169.08, 166.12, 161.24, 158.02, 153.89, 147.67, 138.64, 138.49, 131.64, 127.78, 127.69, 127.44, 127.26, 126.98, 126.66, 113.46, 105.67, 105.31, 71.60, 60.91, 59.01, 48.48, 47.08, 45.18, 41.26, 35.72, 27.97, 22.34.

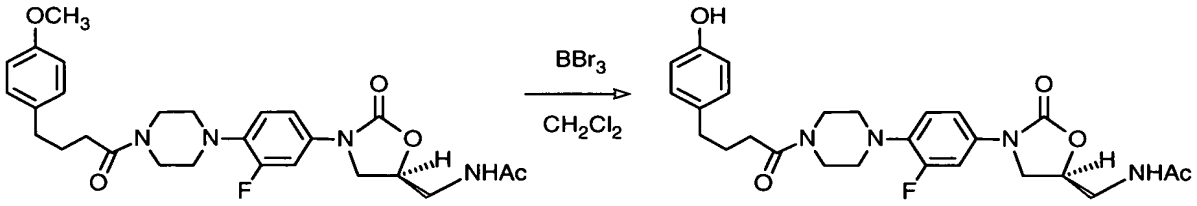
Example 41: N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-methoxyphenyl)butanoyl]piperazine-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (127,). 34709-SCP-137.



17a 127

A stirred mixture of 4-(4-methoxyphenyl)butanoic acid (0.41 g, 2.11 mmol) in pyridine (10 ml), under nitrogen, was treated with EDC (0.48 g, 2.5 mmol), **3** PNU-99388 (0.78 g, 2.1 mmol) and DMAP (10 mg), kept at ambient temperature for 22 h and concentrated *in vacuo*. A mixture of the residue and 5% $NaHCO_3$ was extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from EtOAc gave 0.75 g of **4**: mp 164-165°C; IR (drift) 3307, 1730, 1654, 1630 cm^{-1}. Anal. calcd for $C_{27}H_{33}FN_4O_5$: C, 63.27; H, 6.49; N, 10.93. Found: C, 63.20; H, 6.60; N, 10.95.

Example 42: N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(4-hydroxyphenyl)butanoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (128).



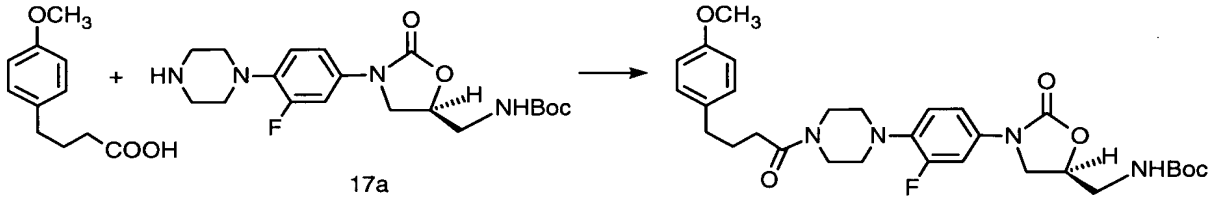
127 128

An ice cold, stirred suspension of **127** (0.25 g, 0.488 mmol) in CH_2Cl_2 (10 ml), under nitrogen, was treated, dropwise during 2 min, with a 1 M solution of boron tribromide in CH_2Cl_2 (1.02 ml). It was warmed to ambient temperature during 2 h, stirred at 0°C for 72 h, warmed to ambient temperature for 4.5 h and mixed with ice water (20 ml). A solution of the resulting gum in CH_2Cl_2 was concentrated and the residue was chromatographed on silica gel with 7% MeOH-CH_2Cl_2. Crystallization of the product from MeOH gave 0.104 g of **128**: mp 119-120°C (dec); ^1H NMR [400 MHz, $(CD_3)_2SO$] δ 1.76 (m, 2H), 1.83 (s, 3H), 2.32 (t, 2H), 2.48 (m, 2H), 2.92 (m, 4H), 3.17

(s, 3H, MeOH), 3.40 (t, 2H), 3.57 (m, 4H), 3.69 (dd, 1H), 4.08 (t, 1H), 4.08 (broad s, 1H), 4.70 (m, 1H), 6.67 (d, 2H), 6.98 (d, 2H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.49 (dd, 1H), 8.25 (t, 1H), 9.13 (s, 1H); MS (ESI+) m/z 499.4 ($M+H^+$), 521 ($M+Na^+$); MS (ESI-) m/z 497.3 (M-H), 533.3 (M+Cl), 577, 579.2, (M+Br); IR (drift) 3273, 3269, 1731, 1643, 1638, cm^{-1}. Anal. calcd for $C_{26}H_{31}FN_4O_5 \cdot CH_3OH$: C, 61.12; H, 6.65; N, 10.56. Found: C, 60.94; H, 6.64; N, 10.56.

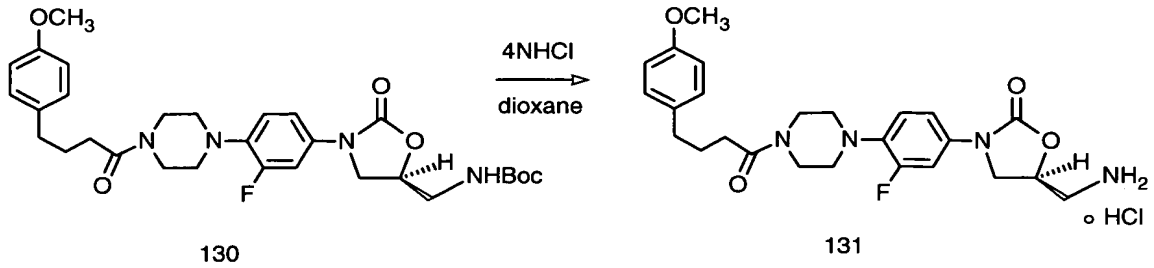
Example 43: 2,2-Difluoro-N-{[(5*S*)-3-(3-fluoro-4-{4-[4-(4-methoxyphenyl)butanoyl] piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}ethanethioamide (129).

Step 1:



A stirred mixture of 4-(4-methoxyphenyl)butanoic acid (0.8 g, 4.1 mmol) and pyridine (20 ml), under nitrogen was treated with EDC (0.96 g, 5.0 mmol), **17a** (1.69 g, 4.28 mmol) and DMAP (20 mg) and kept at ambient temperature for 22 h. It was concentrated *in vacuo* and the residue was mixed with 5% aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2% MeOH-CH_2Cl_2 and crystallization of the product from EtOAc gave 1.26 g of **130**: mp 140-141°C; MS (ESI+) m/z 571.5 ($M+H^+$), 593.5 ($M+Na^+$); MS (ESI-) m/z 569.4 (M-H), 605 (M+Cl).

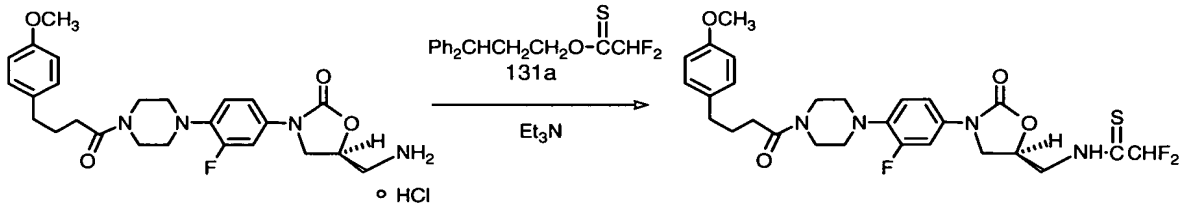
Step 2:



130 131

Compound **130** (0.5 g, 0.88 mmol) was cooled, under nitrogen, in an ice bath and treated, dropwise with stirring during 3 min with 4N HCl in dioxane (7 ml). It was kept in the ice bath for 45 min and at ambient temperature for 90 min. Excess hydrogen chloride was removed under a stream of nitrogen and the mixture was concentrated *in vacuo* to give **131**, a white solid.

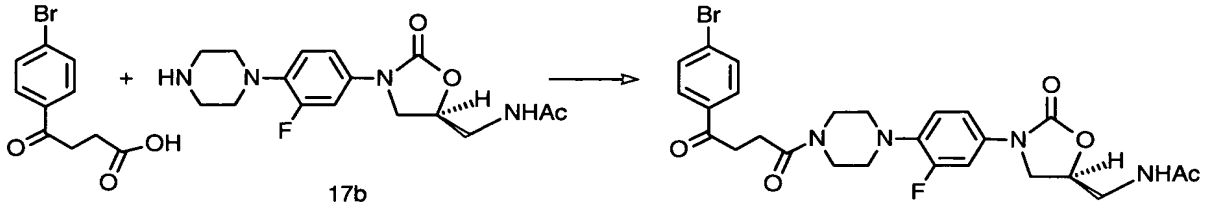
Step 3:



131 129

A stirred mixture of **131** (0.19 g) and CH_2Cl_2 (10 ml), under nitrogen, was treated with triethylamine (0.11 ml) and then, dropwise, with a solution of **131a** (0.15 g, 0.49 mmol) in CH_2Cl_2 (2 ml). It was kept at ambient temperature for 5 h 20 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 1.75% MeOH-CH_2Cl_2 and crystallization of the product from EtOAc-hexane gave 0.14 g of **129**: mp 128-129°C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 1.77 (m, 2H), 2.34 (t, 2H), 2.54 (m, 2H), 2.92 (m, 4H), 3.56, 3.60 (m, m, 4H), 3.71 (s, 3H), 3.82 (dd, 1H), 3.96 (m, 2H), 4.16 (t, 1H), 5.01 (m, 1H), 6.37, 6.50, 6.64 (s, s, s, 1H), 6.85 (d, 2H), 7.10 (m, 3H), 7.18 (dd, 1H), 7.50 (dd, 1H), 11.18 (t, 1H); MS (ESI+) m/z 365.3 ($M+H^+$); MS (ESI-) m/z 563.3 (M-H), 599 (M+Cl); IR (drift) 3274, 1744, 1633, 1617 cm^{-1}. Anal. calcd for $C_{27}H_{31}F_3N_4O_4S$: C, 57.44; H, 5.53; N, 9.92. Found: C, 57.02; H, 5.52; N, 9.83.

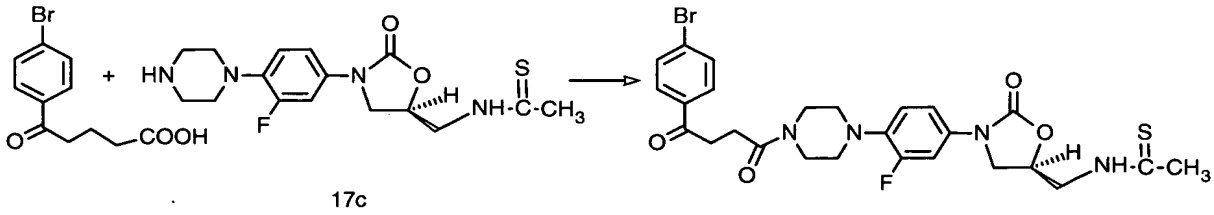
Example 44: N-{[(5*S*)-3-(4-{4-[4-(4-Bromophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (132).



17b 132

A stirred mixture of 3-(4-bromobenzoyl)propionic acid (0.186 g, 0.723 mmol) and pyridine (6 ml), under nitrogen, was treated with EDC (0.13 g, 0.68 mmol), DMAP (10 mg) and **17b**[12] (0.24 g, 0.72 mmol), kept at ambient temperature for 18 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 3% MeOH-$CHCl_3$ and crystallization of the product from CH_3CN gave 0.17 g of **132**: mp 197-198°C; MS (ESI+) m/z 597, 599 ($M+Na^+$); MS (ESI-) m/z 573, 575 (M-H), 609.2, 611.2 (M+Cl); IR (drift) 3311, 1742, 1687, 1647 cm^{-1}. Anal. calcd for $C_{26}H_{28}BrFN_4O_5$: C, 54.27; H, 4.90; N, 9.74. Found: C, 54.29; H, 4.97; N, 9.75.

Example 45: N-{[(5*S*)-3-(4-{4-[4-(4-Bromophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}ethanethioamide (133).

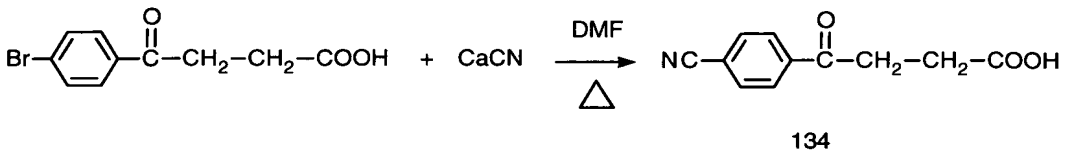


17c 133

A stirred mixture 3-(4-bromobenzoyl)propionic acid (0.186 g, 0.723 mmol) and pyridine (6 ml), under nitrogen, was treated with EDC (0.13 g, 0.68 mmol), DMAP (10 mg) and **17c**[6] (0.25 g, 0.71 mmol), kept at ambient temperature for 18 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 3% MeOH-$CHCl_3$ and crystallization of the product from CH_3CN gave 0.23 g of **133**: mp 219-220°C (dec); MS (ESI+) m/z 613, 615 ($M+Na^+$); MS (ESI-) m/z 589, 591 (M-H), 625.2, 627.2 (M+Cl); IR (drift) 3238, 1755, 1680, 1645, 1620 cm^{-1}. Anal. calcd for $C_{26}H_{28}BrFN_4O_4S$: C, 52.79; H, 4.77; N, 9.47. Found: C, 52.82; H, 4.86; N, 9.86.

Example 46: N-{[(5*S*)-3-(4-{4-[4-(4-Cyanophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (135).

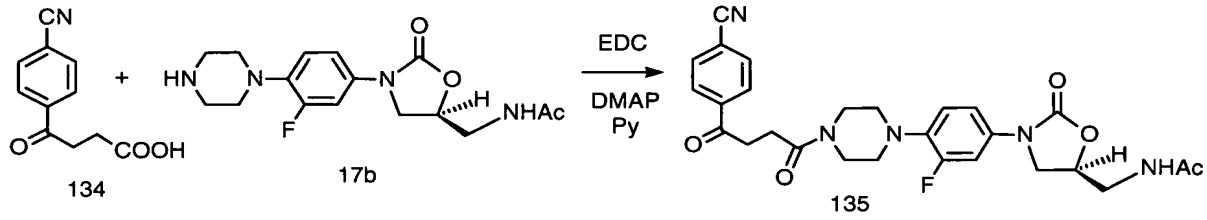
Step 1:



134

According to the method of Curran and Ross[8] a stirred mixture of 3-(4-bromobenzoyl)propionic acid (4.57 g, 0.0178 mol), copper (I) cyanide (1.84 g, 0.0205 mol) and DMF (12 ml) was refluxed, under nitrogen, for 4 h, cooled for 5 min, combined with a mixture of water (12 ml), $FeCl_3 \cdot 6\ H_2O$ (7.8 g) and concentrated HCl (1 ml) and warmed on the steam bath for 20 min. This mixture was poured into water (100 ml) and cooled in an ice bath. The solid was collected by filtration, washed with cold water, and dried *in vacuo*. A portion of this material was chromatographed on silica gel with 2.5% MeOH-0.25% HOAc-CH_2Cl_2 to give 0.7 g of **134**: MS (ESI-) m/z 201.9 (M-H). The remaining product was crystallized from $CHCl_3$ to give 1.23 g of additional **134**.

Step 2:



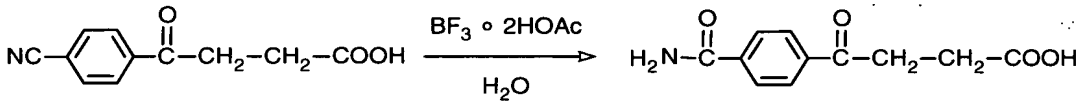
134 17b 135

A stirred mixture of 3-(4-cyanobenzoyl)propionic acid **134** (0.178 g, 0.88 mmol) and pyridine (6 ml), under nitrogen was treated with EDC (0.16 g, 0.83 mmol) and 4-dimethylaminopyridine (10 mg), kept at ambient temperature for 5 min, treated with **61**[12] (0.29 g, 0.862 mmol) and kept at ambient temperature for 3 h and at 10°C for 18 h. It was concentrated *in vacuo* and the residue was chromatographed on silica gel with 2-5% MeOH-CH_2Cl_2. Crystallization of the product from CH_3CN gave 0.261 g of **135**: mp 197-198°C; MS (ESI+) m/z 522.2 ($M+H^+$), 544 ($M+Na^+$); MS (ESI-) m/z 520.1 (M-H), 556.0 (M+Cl); IR (drift) 3296, 2234, 1757, 1693, 1640 cm^{-1}; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.06 (s, 1.4H, CH_3CN), 2.77 (t, 2H), 2.89, 2.99

(s, s, 4H), 3.25 (t, 2H), 3.38 (t, 2H), 3.57 (s, 2H), 3.66 (m, 3H), 4.07 (t, 1H), 4.68 (m, 1H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.49 (dd, 1H), 8.00 (d, 2H), 8.11 (d, 2H), 8.23 (t, 1H); HRMS (FAB) calcd for $C_{27}H_{29}FN_5O_5$ ($M+H^+$) 522.2153, found 522.2139. Anal. calcd for $C_{27}H_{28}FN_5O_5 \circ 0.5\ CH_3CN$: C, 62.04; H, 5.48; N, 14.21. Found: C, 61.31; H, 5.57; N, 13.95.

Example 47: 4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}benzamide (137).

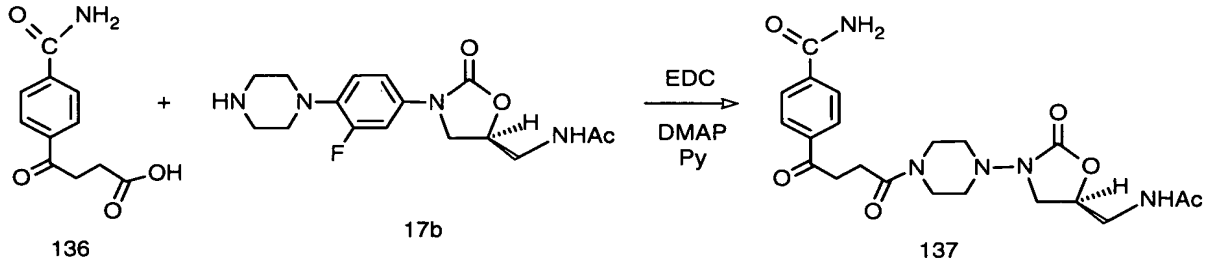
Step 1:



134 136

A mixture of boron trifluoride-acetic acid complex (0.74 ml, 5.3 mmol) and water (0.09 ml, 5.0 mmol) was added, under nitrogen with stirring to **134** (0.20 g, 0.98 mmol) and the resulting mixture was warmed in an oil bath at 130°C for 10 min, kept at ambient temperature for 1 h and rewarmed at 130°C for 5 min. It was then concentrated under a stream of nitrogen. The residue was mixed with CH_2Cl_2 and MeOH to give 0.17 g of **136**, a white solid: MS (ESI+) m/z 221.9 ($M+H^+$), 244.0 ($M+Na^+$); MS (ESI-) m/z 220 (M-H).

Step 2:

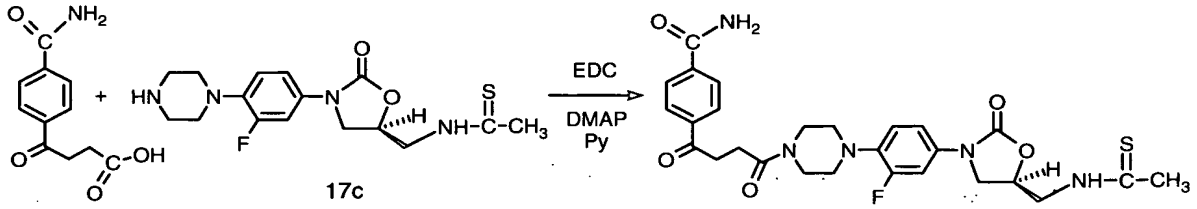


136 17b 137

A stirred mixture of **136** (0.16 g, 0.72 mmol) and pyridine (6 ml) under nitrogen was treated with EDC (0.13 g, 0.68 mmol), DMAP (10 mg) and **17b**[12] (0.24 g, 0.71 mmol) and kept at ambient temperature for 20 h. It was then concentrated *in vacuo* and the residue was chromatographed on silica gel with 7-10% MeOH-CH_2Cl_2. Crystallization of the product from MeOH-CH_2Cl_2 gave 0.219 g of **137**: mp > 250°C;

IR (drift) 3394, 3335, 3199, 1746, 1727, 1697, 1676, 1630 cm^{-1}. Anal. calcd for $C_{27}H_{30}FN_5O_6$: C, 60.10; H, 5.60; N, 12.98. Found: C, 59.60, 59.78; H, 5.64, 5.64; N, 12.77, 12.91.

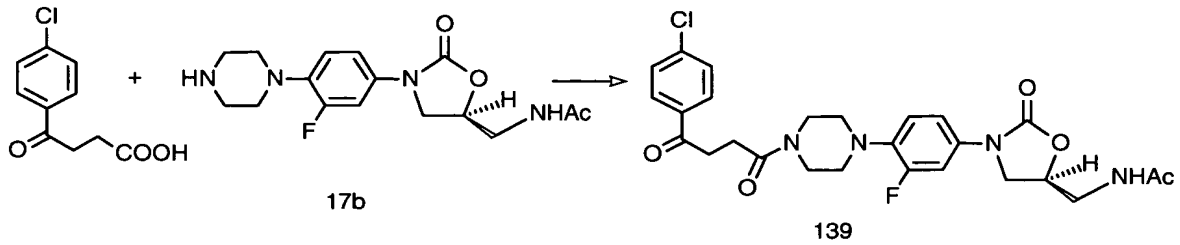
Example 48: 4-{4-[4-(4-{(5*S*)-5-[(Ethanethiolylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}benzamide 138.



136 17c 138

A stirred mixture of **136** (0.16 g, 0.72 mmol) in pyridine (6 ml) under nitrogen, was treated with EDC (0.13 g, 0.68 mmol) and DMAP (10 mg), kept at ambient temperature for 5 min and treated with **17c**[6] (0.25 g, 0.71 mmol). It was kept at ambient temperature for 2.5 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 6% MeOH-CH_2Cl_2 and crystallization of the product from CH_3CN gave 0.11 g, mp 219-220°C (dec) and 0.13 g, mp 223-224°C (dec) of **138**: IR (drift) 3374, 3301, 3290, 3253, 3195, 1738, 1679, 1661, 1620 cm^{-1}. Anal. calcd for $C_{27}H_{30}FN_5O_5S$: C, 58.37; H, 5.44; N, 12.60. Found: C, 58.22; H, 5.46; N, 12.70.

Example 49: N-{[(5*S*)-3-(4-{4-[4-(4-Chlorophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide 139.

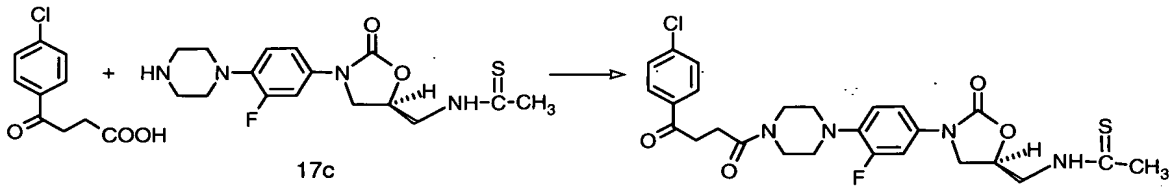


17b 139

A stirred mixture of 3-(4-chlorobenzoyl)propionic acid (0.153 g, 0.72 mmol) in pyridine (6 ml), under nitrogen, was treated with EDC (0.14 g, 0.73 mmol), DMAP

(10 mg) and **17b**[12] (0.24 g, 0.72 mmol), kept at ambient temperature for 20 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ and crystallization of the product from CH_3CN gave 0.256 g of **139**: mp 208-209°C; IR (drift) 3328, 1741, 1672, 1645, 1625 cm^{-1}. Anal. calcd for $C_{26}H_{28}ClFN_4O_5$: C, 58.81; H, 5.32; N, 10.55. Found: C, 58.78; H, 5.36; N, 10.54.

Example 50: N-{[(5*S*)-3-(4-{4-[4-(4-chlorophenyl)-4-oxobutanoyl]-1-piperazinyl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}ethanethioamide 140.



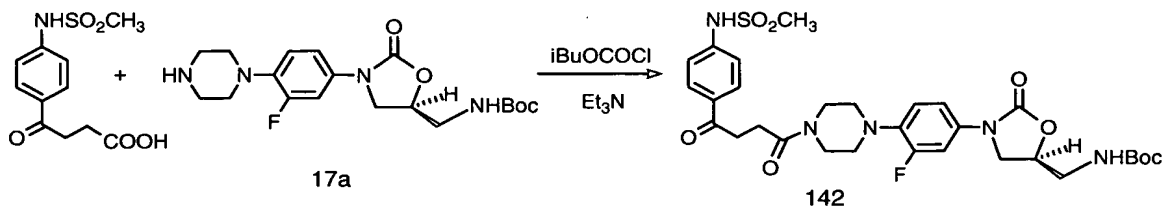
17c

140

A stirred mixture of 3-(4-chlorobenzoyl)propionic acid (0.153 g, 0.720 mmol) in pyridine (6 ml), under nitrogen was treated with EDC (0.13 g, 0.68 mmol), DMAP (10 mg) and **17c**[6] (0.25 g, 0.71 mmol), kept at ambient temperature for 20 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2% MeOH-CH_2Cl_2 and crystallization of the product from CH_3CN gave 0.226 g of **140**: mp 215-216°C (dec); IR (drift) 3235, 1755, 1679, 1620 cm^{-1}. Anal. calcd for $C_{26}H_{28}ClFN_4O_4S$: C, 57.08; H, 5.16; N, 10.24. Found: C, 57.09; H, 5.24; N, 10.43.

Example 51: N-[((5*S*)-3-{3-Fluoro-4-[4-(4-{4-[(methylsulfonyl)amino]phenyl}-4-oxobutanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide 141.

Step 1:

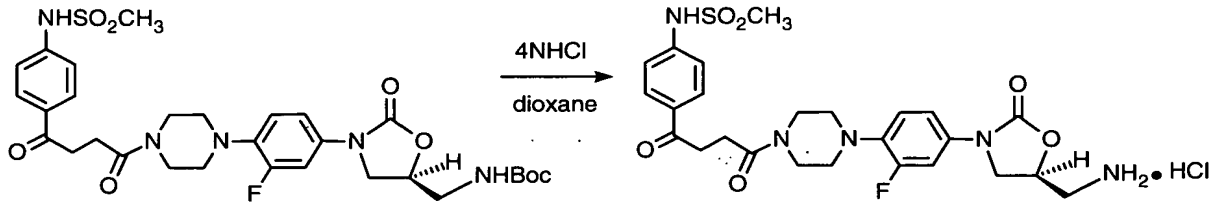


17a

142

A stirred mixture of PNU-68849 4-[(methylsulfonyl)amino]-□-oxo-Benzenebutanoic acid, (0.583 g, 2.15 mmol) and triethylamine (0.35 ml) in THF (20 ml), under nitrogen, was cooled in an ice-MeOH bath and treated, dropwise with isobutyl chloroformate (0.33 ml). It was kept in the bath for 30 min and then treated with a mixture of **17a**[5] (0.85 g, 2.15 mmol), triethylamine (0.35 ml) and THF (15 ml). This mixture was kept at 0°C for 90 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2% MeOH-CH_2Cl_2 and crystallization of the product from CH_3CN gave 0.64 g, mp 171-173°C (dec) and 0.151 g, mp 173-175°C (dec) of **142**: MS (ESI) 670.3 ($M+Na^+$).

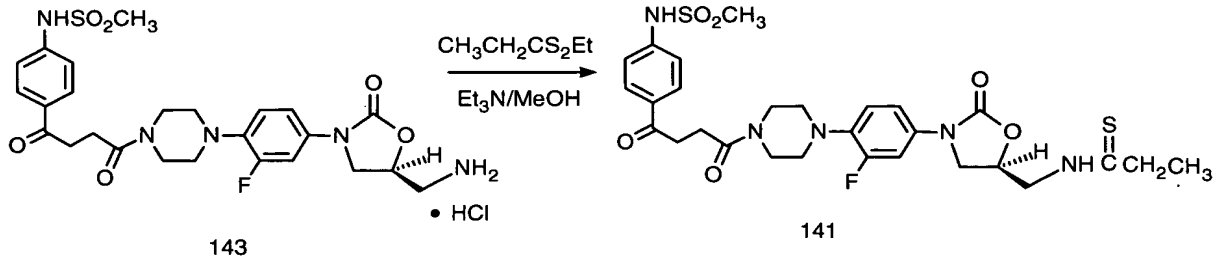
Step 2:



142 143

A stirred solution of **142** (0.42 g, 0.65 mmol) in dioxane (8 ml) was cooled in an ice bath and treated, dropwise during 4 min, with ice cold 4N HCl in dioxane (6 ml). The mixture was kept in the ice bath for 1 h, at ambient temperature for 3 h and at 4°C for 18 h. It was then concentrated *in vacuo* to give 0.4 g of **143**: MS (ESI) m/z 548.2 ($M+H^+$).

Step 3:

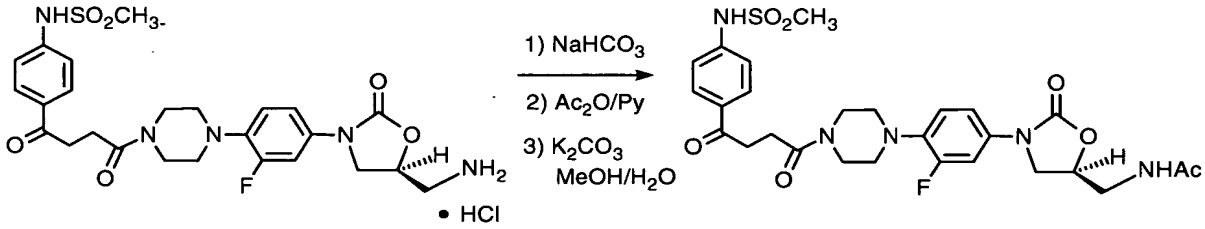


143 141

A stirred mixture of **143** (0.16 g), triethylamine (0.15 ml, 1.08 mmol) and MeOH (10 ml), under nitrogen, was treated with ethyl dithiopropionate (0.05 ml, 0.39 mmol), kept at ambient temperature for 3 h and concentrated *in vacuo*. The residue was found to be a mixture of starting material and product. It was mixed with MeOH (6 ml), triethylamine (0.1 ml) and ethyl dithiopropionate (0.04 ml) and stirred at ambient temperature for 6 h. This mixture was concentrated and the residue was chromatographed on silica gel with 2% MeOH-CH_2Cl_2. Crystallization of the product

from MeOH gave 0.07 g of **141**: mp 201-202°C (dec) with softening at 198°C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.13 (t, 3H), 2.57 (q, 2H), 2.71 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.09 (s, 3H), 3.18 (t, 2H), 3.57, 3.64 (s, s, 4H), 3.78 (dd, 1H), 3.90 (t, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.08 (t, 1H), 7.17 (dd, 1H), 7.28 (d, 2H), 7.50 (dd, 1H), 7.95 (d, 2H), 10.31 (s, 1H); MS (ESI) m/z 642.2 ($M+Na^+$); HRMS (FAB) calcd for $C_{28}H_{35}FN_5O_6S_2$ ($M+H^+$) 620.2012, found 620.2006; IR (drift) 3301, 3177, 3159, 1747, 1674, 1630 cm^{-1}.

Example 52: N-[((5*S*)-3-{3-Fluoro-4-[4-(4-{4-[(methylsulfonyl)amino]phenyl}-4-oxobutanoyl-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide 144.



143 144

A sample of **143** (prepared from 0.35 g, 0.54 mmol of **17a**) was stirred with a mixture of Et_2O (5 ml) and 5% $NaHCO_3$ (10 ml) and concentrated under a stream of nitrogen. The resulting solid was collected by filtration, washed with water and dried to give 0.23 g of the free base. A stirred suspension of this material in pyridine (3 ml), under nitrogen, was cooled in an ice bath and treated with acetic anhydride (0.16 ml). It was kept in the ice bath for 1 h and at ambient temperature for 2.5 h and then concentrated *in vacuo*. The product was found to be a mixture of **144** and a compound in which both the amine and the sulfonamide nitrogen had been acetylated. A solution of the residue in MeOH was therefore hydrolyzed with 10% aqueous K_2CO_3 (2 ml). When the reaction was complete the mixture was concentrated and the residue was mixed with water, neutralized with 10% $KHSO_4$ and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 3-5% MeOH-CH_2Cl_2 and crystallization of the product from MeOH gave 0.102 g of **144**: mp 220-222°C (dec); MS (ESI) m/z 590.3 ($M+H^+$), 612 ($M+Na^+$); IR (drift) 3374, 3348, 3168, 3154, 1759, 1674, 1623, 1602 cm^{-1}; HRMS (FAB) calcd for

$C_{27}H_{33}FN_5O_7S$ ($M+H^+$) 590.2084, found 590.2098. Anal. calcd for $C_{27}H_{32}FN_5O_7S$: C, 55.00; H, 5.47; N, 11.88. Found: C, 54.72; H, 5.55; N, 11.78.

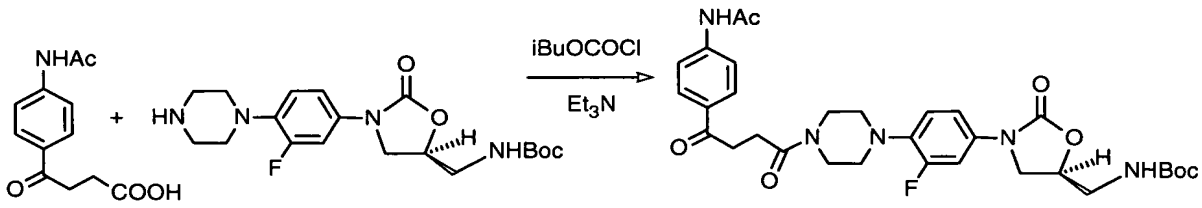
Example 53: N-(4-{4-[4-(2-Fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)acetamide 145.

Step 1:

146

Dimethylformamide (19.1 ml) was added, dropwise during 30 min, under nitrogen with stirring to aluminum chloride (116.5 g). The addition was exothermic and gave a semiliquid mass. This mixture was warmed in an oil bath at 70°C and treated, portionwise during 10 min, with a mixture of acetanilide (12.5 g, 0.0925 mol) and succinic anhydride (8.35 g, 0.0834 mol). It was kept at 70-72°C for 1 h and then poured into ice (800 g). The resulting solution was treated with a mixture of concentrated HCl (50 ml) and ice (50 g) to give a precipitate which was collected by filtration washed with cold water and dried. Crystallization of the solid from acetonitride gave 10.7 g of **146**: MS (ESI) m/z 236.1 ($M+H^+$), 258.1 ($M+Na^+$).

Step 2:

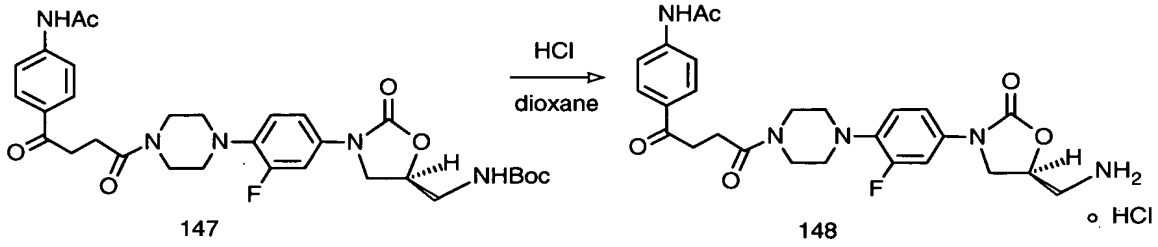


146 17a 147

A stirred mixture of **146** (1.01 g, 4.29 mmol) and triethylamine (0.69 ml, 4.96 mmol) in THF (20 ml), under nitrogen was cooled in an ice-MeOH bath and treated, dropwise with isobutyl chloroformate (0.66 ml, 5.1 mmol). It was kept in the bath for 30 min and then treated, in portions during 4 min, with a mixture of **17a**[5] (1.69 g, 4.28

mmol), triethylamine (0.69 ml, 4.96 mmol) and THF (15 ml). The mixture was allowed to warm to 10°C during 2 h when it was concentrated *in vacuo*. A mixture of the residue and CH_2Cl_2 was washed with saturated $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave 1.84 g of **147**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.34 (s, 9H), 2.07 (s, 3H), 2.71 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.18 (t, 2H), 3.25 (t, 2H), 3.57, 3.66 (s, s, 4H), 3.75 (dd, 1H), 4.06 (t, 1H), 4.66 (m, 1H), 7.07 (t, 1H), 7.18 (m, 2H), 7.48 (dd, 1H), 7.69 (d, 2H), 7.93 (d, 2H), 10.28 (s, 1H); MS (ESI) m/z 612.3 ($M+H^+$), 634.2 ($M+Na^+$).

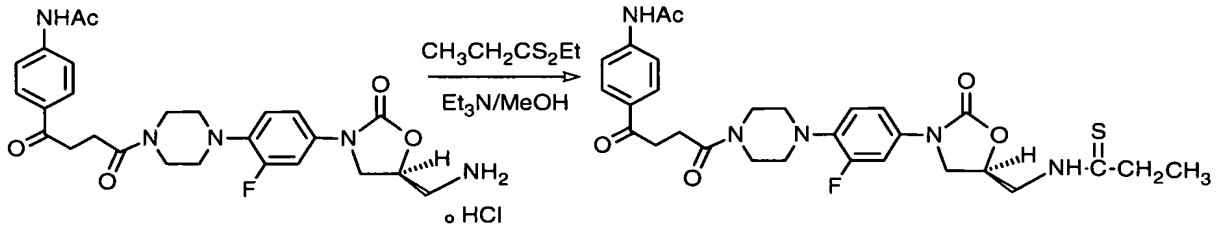
Step 3:



147 148

A stirred mixture of **147** (1.0 g, 1.63 mmol) in dioxane (25 ml), under nitrogen was cooled in an ice bath and treated with ice-cold 4N hydrogen chloride in dioxane (10 ml). It was kept in the ice bath for 1.5 h, at ambient temperature for 4 h and at 0°C for 14 h. It was then kept at ambient temperature for 2 h and concentrated *in vacuo* to give 1.04 g of **148**, a white powder.

Step 4:



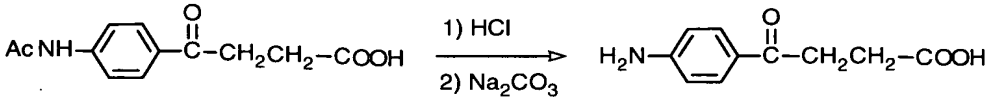
148 145

A stirred mixture of **148** (0.51 g), triethylamine (0.37 ml, 2.7 mmol) and MeOH (20 ml), under nitrogen, was treated with ethyl dithiopropionate (0.13 ml, 1.02 mmol), kept at ambient temperature for 4 h and concentrated under a stream of nitrogen for 1 h. The solid product was collected by filtration, and the filtrate was concentrated

under a stream of nitrogen. Trituration of the residue with MeOH gave additional product. Chromatography of the combined product on silica gel with 2.5% MeOH-CH_2Cl_2 and crystallization from MeOH gave 0.326 g of **145**: mp 198-199°C (dec) with softening at 195°C; MS (ESI) m/z 584.3 ($M+H^+$), 606.3 ($M+Na^+$); IR (drift) 3258, 3193, 1742, 1697, 1678, 1615 cm^{-1}. Anal. calcd for $C_{29}H_{34}FN_5O_5S$: C, 59.68; H, 5.87; N, 12.00. Found: C, 59.45; H, 5.94; N, 11.94.

Example 54: 2-Amino-N-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)acetamide 149.

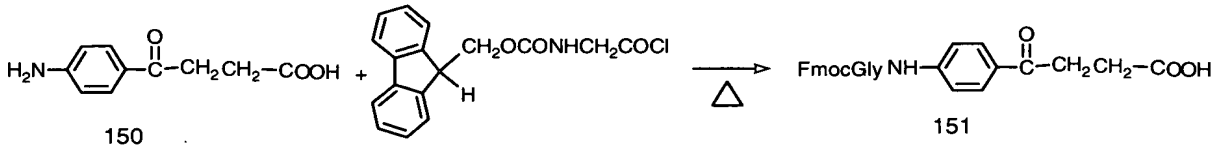
Step 1:



146 150

A mixture of **146** (4.97 g, 0.021 mol) and concentrated HCl (35 ml) was warmed on the steam bath for 20 min and the resulting solution was placed under a stream of nitrogen for 30 min. The resulting mixture was diluted with water (50 ml) and adjusted to pH 4 with solid Na_2CO_3. The solid product was collected by filtration, washed with water and dried *in vacuo* at 50°C to give 3.95 g of **150** which could be recrystallized from acetonitrile. A second crop, 0.31 g of **150** was obtained from the aqueous filtrate.

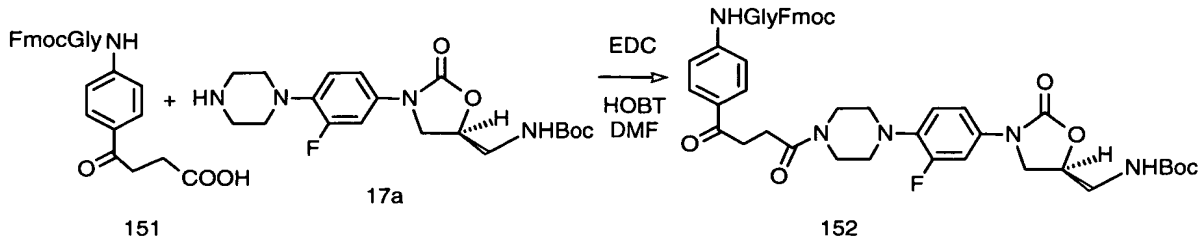
Step 2:



150 151

A stirred mixture of **150** (0.47 g, 0.00243 mol), N-Fmoc-glycyl chloride (0.85 g, 0.0027 mol) and THF (50 ml) was refluxed, under nitrogen for 4 h and cooled to ambient temperature. The solid was collected by filtration to give 0.18 g of **151**. Concentration of the mother liquor gave an additional 1.14 g of **151**: MS (ESI+) m/z 495 (M+Na); MS (ESI-) m/z 471 (M-H).

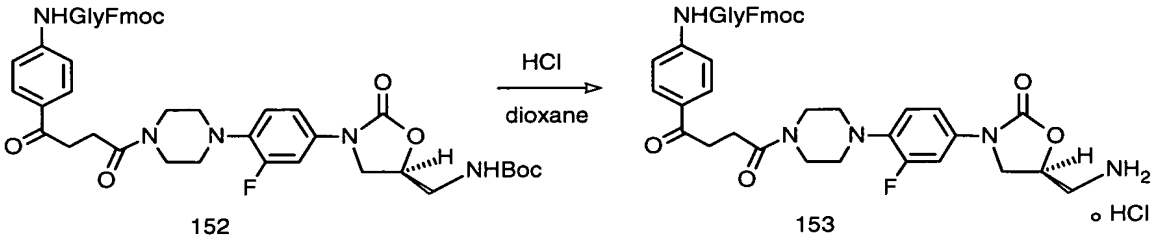
Step 3:



151 152

An ice cold, stirred mixture of **151**(0.17 g, 0.36 mmol) and DMF (3 ml), under nitrogen was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.08 g, 0.42 mmol) and 1-hydroxybenzotriazole hydrate (0.05 g, 0.37 mmol), kept for 20 min and then treated with **17a**[5] (0.14 g, 0.35 mmol) in portions during 10 min. The mixture was kept in the ice bath for 1 h 45 min and at ambient temperature for 45 min and then concentrated *in vacuo*. Chromatography of the semisolid residue on silica gel with 2% MeOH-CH_2Cl_2 gave 0.18 g of **152**: MS (ESI-) m/z 883.2 (M+Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.81 (m, 2H), 3.16 (s, s, 2H), 3.38 (m, 4H), 3.54 (m, 4H), 3.79 (m, 3H), 4.04 (m, 4H), 4.16 (s, 3H), 4.25 (t, 1H), 4.50 (d, 2H), 4.78 (m, 1H), 5.03 (m, 1H), 5.64 (m, 1H), 7.04 (m, 1H), 7.32 (m, 3H), 7.42 (m, 3H), 7.61 (m, 5H), 7.77 (m, 3H), 7.96 (m, 3H), 8.57 (m, 1H).

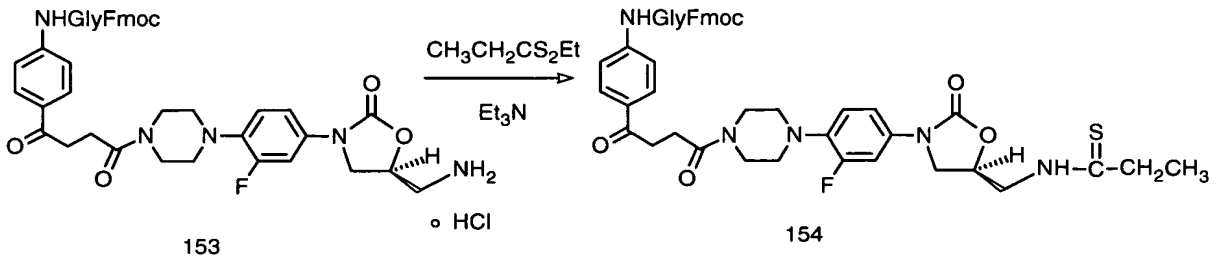
Step 4:



152 153

A stirred suspension of **152** (0.34 g, 0.4 mmol) in dioxane (24 ml), under nitrogen was treated with ice cold 4N HCl in dioxane (6 ml) with cooling in an ice bath. It was kept in the ice bath for 1.25 h, at ambient temperature for 3 h, at 0°C for 18 h and at ambient temperature for 6 h. It was then placed under a stream of nitrogen for 30 min and concentrated *in vacuo* to give **7153**.

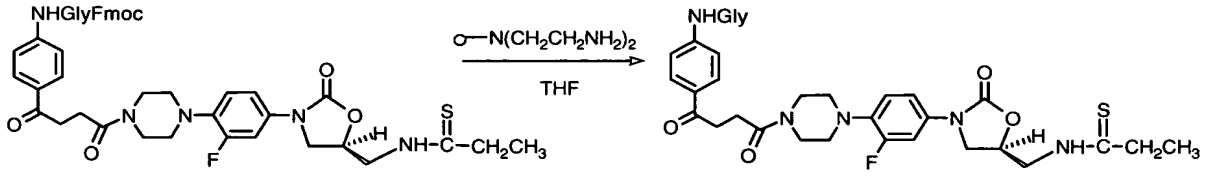
Step 5:



153 154

A stirred mixture of **153** from the previous reaction, ethyl dithiopropionate (0.073 ml) and triethylamine (0.22 ml) in MeOH (15 ml), under nitrogen, was kept at ambient temperature for 2 h, treated with additional MeOH (15 ml) and kept at ambient temperature for 21 h. The reaction was still not complete. The mixture was treated with additional triethylamine (0.1 ml) and kept for 24 h; it was then treated with additional ethyl dithiopropionate (0.07 ml) and kept at ambient temperature for 6 h and at 0°C for 72 h. It was concentrated under a stream of nitrogen for 7 h and then *in vacuo*. Chromatography of the residue on silica gel with 1.5-3% MeOH-CH_2Cl_2 gave 0.09 g of **154**: MS (ESI-) m/z 819 (M-H), 855 (M+Cl).

Step 6:

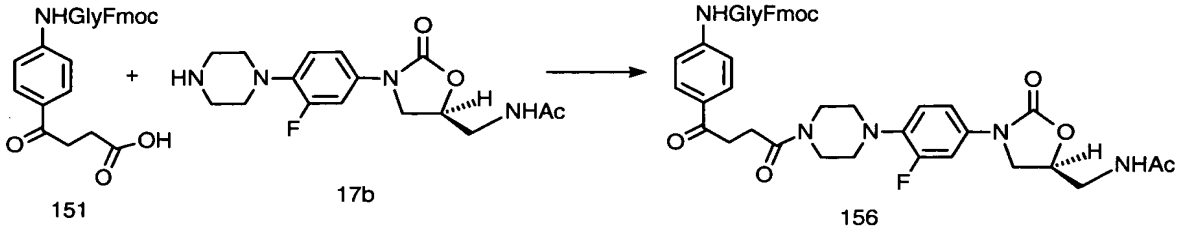


154 149

A stirred mixture of **154** (0.10 g, 0.12 mmol), "trisamine" resin (0.12 g, 0.48 mmol) and THF (10 ml) was refluxed, under nitrogen for 5 h, kept at ambient temperature for 18 h and refluxed for 4 h. It was filtered, the solid was washed with THF and MeOH and the filtrate was concentrated *in vacuo*. Chromatography of the residue over silica gel with 4% MeOH-0.25% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH-EtOAc gave 0.0516 g of **149**, mp 197-198°C (dec): MS (ESI+) m/z 599.3 ($M+H^+$); MS (ESI-) m/z 633.0 (M+Cl-); IR (drift) 3283, 1736, 1680, 1644, 1630 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{36}FN_6O_5S$ ($M+H^+$) 599.2452, found 599.2471.

Example 55: N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)-2-aminoacetamide 155.

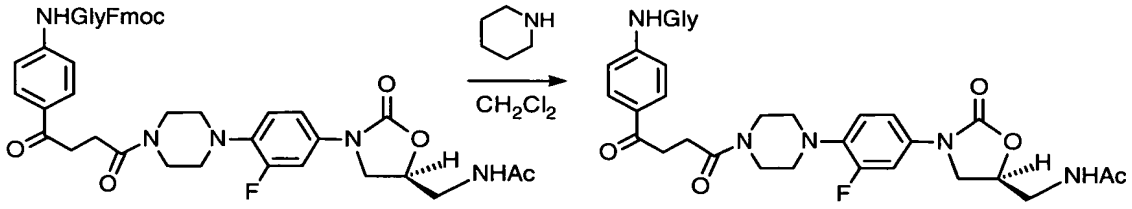
Step 1:



151 17b 156

A stirred mixture of **151** (0.19 g, 0.40 mmol), EDC (0.08 g, 0.42 mmol) and HOBT(0.05 g, 0.37 mmol) in DMF (3 ml), under nitrogen, was kept at ambient temperature for 30 min and treated with **17b**[12] (0.12 g, 0.36 mmol). It was kept at ambient temperature for 18 h, treated with additional EDC (0.08 g) and HOBT (0.05 g), and kept at ambient temperature for 72 h. This mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel with 2.5-4% MeOH-CH_2Cl_2 to give 0.06 g of **156**: MS (ESI-) m/z 825.2 ($M+Cl^-$); ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.71 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.19 (t, 2H), 3.38 (t, 2H), 3.55 (s, 2H), 3.66 (m, 3H), 3.82 (d, 2H), 4.07 (t, 1H), 4.27 (m, 3H), 4.67 (m, 1H), 7.08 (t, 1H), 7.18 (dd, 1H), 7.40 (m, 6H), 7.70 (m, 5H), 7.95 (m, 4H), 8.21 (t, 1H).

Step 2:



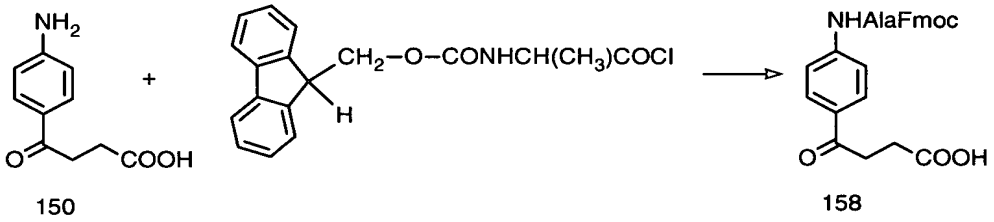
156 155

A stirred mixture of **156** (0.15 g, 0.19 mmol) and CH_2Cl_2 (5 ml), under nitrogen was treated with piperidine (0.06 ml, 0.61 mmol) and kept at ambient temperature for 3.5 h. Additional piperidine (0.2 ml) was added and the mixture was kept at ambient temperature for 24 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 8% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH-EtOAc gave 0.0459 g of **155**: mp 221-222°C (dec); MS (ESI+) m/z 569.3 ($M+H^+$); MS (ESI-) m/z 603.2 ($M+Cl^-$); IR (drift) 3322, 3297, 1742, 1687, 1645

cm^{-1}; ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 2.71 (t, 2H), 2.89, 2.99 (s, s, 4H), 3.19 (t, 2H), 3.30 (m, 5H), 3.38 (t, 2H), 3.57 (s, 2H), 3.66 (m, 3H), 4.07 (t, 1H), 4.69 (m, 1H), 7.07 (t, 1H), 7.16 (dd, 1H), 7.48 (dd, 1H), 7.77 (d, 2H), 7.95 (d, 2H), 8.23 (t, 1H); HRMS (FAB) calcd for $C_{28}H_{34}FN_6O_6$ ($M+H^+$) 569.2524, found 569.2529.

Example 56: N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutanoyl}phenyl)-(2*S*)-2-aminopropanamide 157.

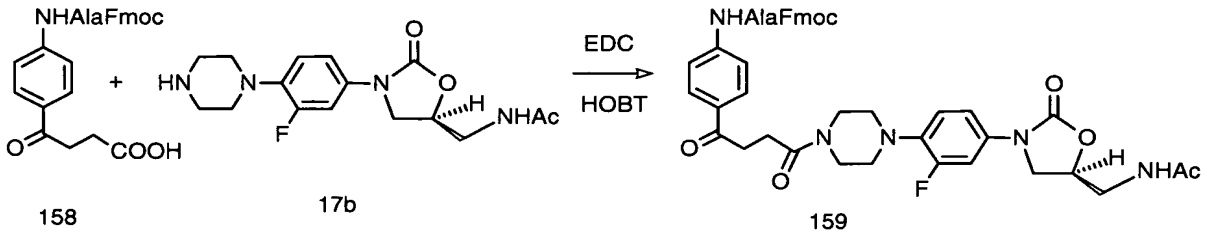
Step 1:



150 158

A stirred mixture of **22** (0.50 g, 2.59 mmol) and (*S*)-N-Fmoc-alanyl chloride (0.939 g, 2.85 mmol) in THF (50 ml) was refluxed under nitrogen for 2 h, cooled and filtered. The filtrate was concentrated and the residue was crystallized from acetonitrile to give 0.78 g, mp 211-212°C and 0.20 g, mp 210-211°C of **24**: MS (ESI+) m/z 309.2 ($M+Na^+$); MS (ESI-) m/z 485.1 (M-H), 521.0 (M+Cl).

Step 2:

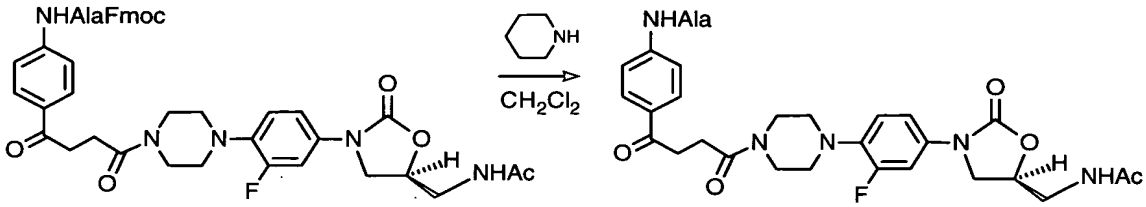


158 17b 159

A mixture of **158** (0.35 g, 0.72 mmol), EDC (0.15 g, 0.78 mmol), HOBT (0.10 g, 0.74 mmol) and DMF (6 ml) was stirred under nitrogen for 15 min, treated with **17b**[12] (0.24 g, 0.71 mmol) and kept at ambient temperature for 22 h. By TLC a considerable amount of **17b** remained in the reaction mixture. It was treated with a mixture of **158**

(0.175 g), EDC (0.075 g), HOBT (0.05 g) and DMF (2 ml) that had been prepared, under nitrogen, in a separate flask and stirred for 30 min. The resulting mixture was kept at ambient temperature for 72 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 3% MeOH-CH_2Cl_2 gave 0.14 g of **159**: MS (ESI-) m/z 839.2 (M+Cl).

Step 3:

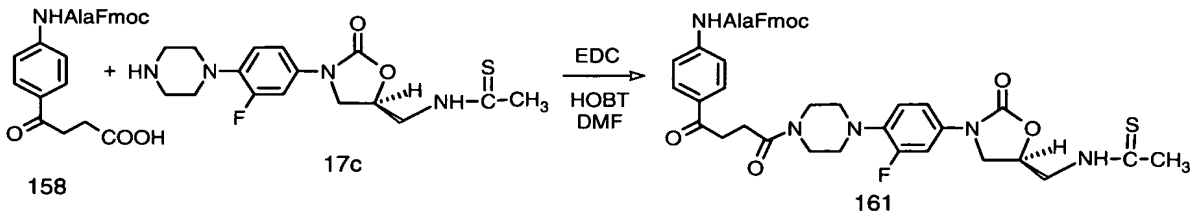


159 157

A stirred suspension of **159** (0.11 g, 0.14 mmol) in CH_2Cl_2 (20 ml), under nitrogen was treated with piperidine (0.3 ml) and kept at ambient temperature for 18 h. The resulting solution was concentrated *in vacuo* and the residue was chromatographed on silica gel with 4% MeOH-0.25% NH_4OH-CH_2Cl_2. A solution of the product in MeOH-CH_2Cl_2 was concentrated *in vacuo* to give 0.048 g of **157** as a foam: MS (ESI+) m/z 583.3 ($M+H^+$); MS (ESI-) m/z 617.1 ($M+Cl^-$); IR (drift) 3300, 1751, 1749, 1677, 1647 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{36}FN_6O_6$ ($M+H^+$) 583.2680, found 583.2682.

Example 57 N-1-(4-{4-[4-(4-{(5*S*)-5-[(Ethanethiolylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}phenyl)-(*S*)-alaninamide 160.

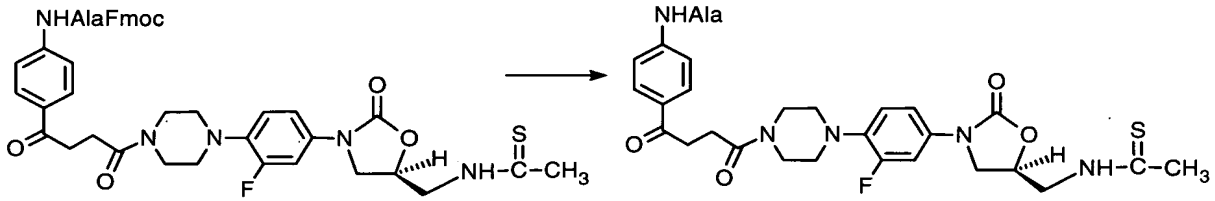
Step 1:



158 17c 161

A stirred mixture of **158** (0.213 g, 0.438 mmol) in DMF (2.5 ml), under nitrogen, was treated with EDC (0.084 g, 0.438 mmol) and HOBT (0.05 g, 0.375 mmol), kept at ambient temperature for 10 min and treated with **17c**[6] (0.123 g, 0.349 mmol). It was kept at ambient temperature for 18 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 3% MeOH-CH_2Cl_2 gave 0.29 g of **161**: MS (ESI-) m/z 855.3 (M+Cl).

Step 2:

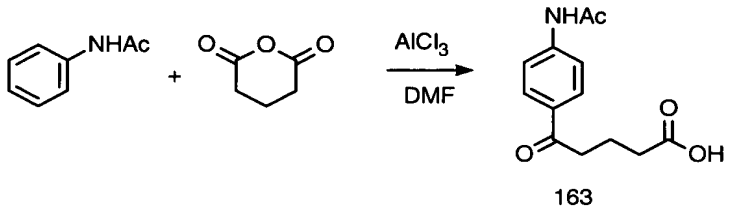


161 160

A stirred mixture of **161** (0.29 g, 0.35 mmol) and CH_2Cl_2 (45 ml), under nitrogen was treated with piperidine (0.8 ml) and kept at ambient temperature for 22 h. It was concentrated *in vacuo* and the residue was crystallized from CH_3CN. The solid was collected by filtration and the filtrate was concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-CH_2Cl_2 and crystallization from CH_3CN gave 0.0675 g of **160**: MS (ESI+) m/z 599.4 ($M+H^+$); MS (ESI-) m/z 597.4 (M-H), 633.3 (M+Cl); IR (drift) 3243, 3280, 3176, 1753, 1750, 1685, 1681, 1645, 1630 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{36}FN_6O_5S$ ($M+H^+$) 599.2452, found 599.2454.

Example 58: N^1-[4-(5-{4-[4-((5*S*)-5-{[(2,2-Difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]piperazin-1-yl}-5-oxopentanoyl)phenyl]glycinamide 162.

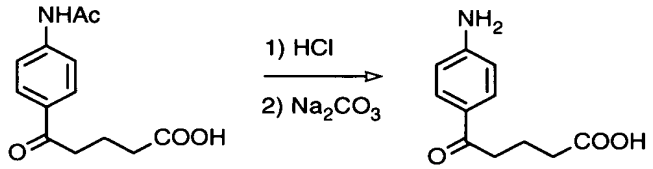
Step 1:



163

Dimethylformamide (9.6 ml) was added, dropwise with stirring under nitrogen during 30 min to aluminum chloride (58.25 g) and the resulting mixture was warmed in a bath at 75°C and treated, portionwise during 8 min, with a mixture of acetanilide (6.25 g, 0.0462 mol) and glutaric anhydride (4.75 g, 0.0417 mol). The mixture was kept at 72-75°C for 1 h and then mixed with ice. The resulting stirred mixture was treated with a mixture of concentrated hydrochloric acid (25 ml) and ice (25 g). The product was collected by filtration, washed with cold water, dried and crystallized from acetonitrile to give 2.0 g of **163**, mp 185-186°C. MS (ESI+) m/z 250.2 ($M+H^+$), 272.2 ($M+Na^+$), 288.1 ($M+K^+$); MS (ESI-) m/z 248.1 (M-H), 284.1 (M+Cl).

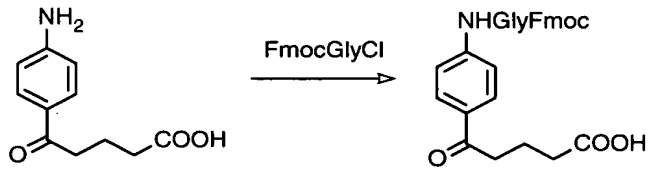
Step 2:



163 164

A mixture of **163** (2.0 g, 8.0 mmol) and concentrated hydrochloric acid (10 ml) was warmed on the steam bath for 20 min and cooled under a stream of nitrogen for 20 min. It was then diluted with water (20 ml) and adjusted to pH 5 with solid Na_2CO_3. The mixture was cooled and the solid product was collected by filtration, washed with cold water and dried *in vacuo* to give **164**: MS (ESI+) m/z 208.1 (M+H), 230.2 ($M+Na^+$); MS (ESI-) m/z 206.1 (M-H), 242.1 (M+Cl).

Step 3:

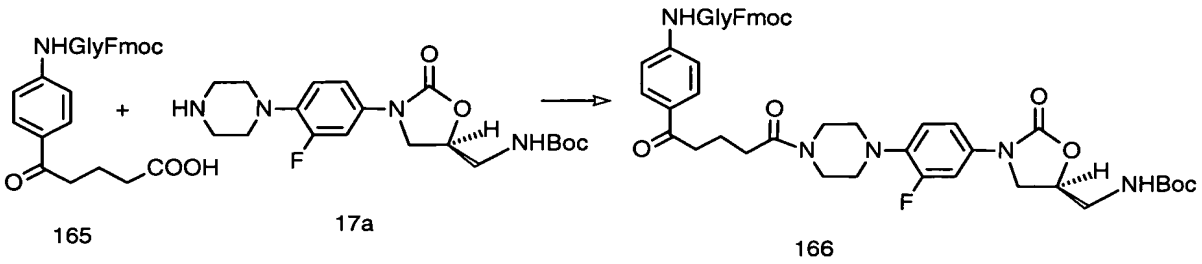


164 165

A stirred mixture of **23** (0.50 g, 2.4 mmol) and N-Fmoc-glycyl chloride (0.85 g, 2.7 mmol) in THF (50 ml) was refluxed, under nitrogen, for 4 h, cooled and diluted with CH_2Cl_2 (50 ml). The white precipitate was collected by filtration to give 0.93 g of **25**: mp 217-218°C; MS (ESI-) m/z 485.2 (M-H), 521.2 (M+35). The filtrate was

concentrated and the residue was mixed with Et_2O and filtered to give 0.20 g of additional **83**, mp 215-216°C.

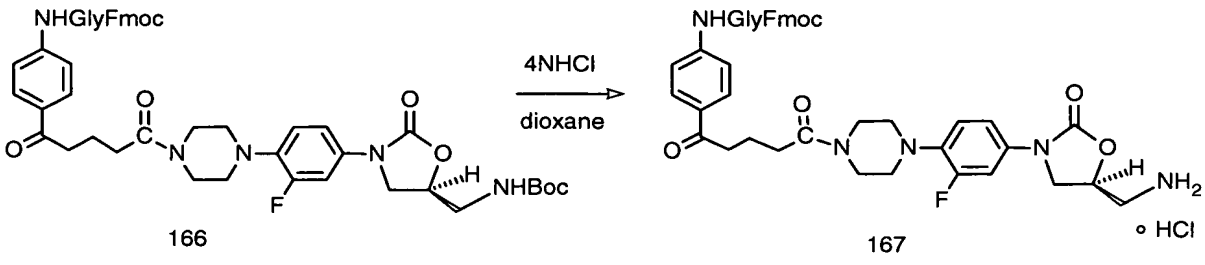
Step 4:



165 17a 166

A stirred mixture of **165** (0.486 g, 0.999 mmol), **17a** (0.4 g, 1.0 mmol) and pyridine (7 ml), under nitrogen, was treated with EDC (0.25 g, 1.3 mmol) and DMAP (10 mg) and kept at ambient temperature for 24 h. It was concentrated *in vacuo* and the residue was stored under a stream of nitrogen for 2 d. During this period it appeared (MS) that a considerable amount of the Fmoc protecting group had been removed. The residue was mixed with water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated to give 0.45 g of a mixture of **166** and the Fmoc deprotected material. A stirred mixture of this material in THF (20 ml), under nitrogen, was treated with diisopropylethylamine (0.13 ml, 0.77 mmol) and Fmoc chloride (0.14 g, 0.54 mmol) and kept at ambient temperature for 2.5 h. It was concentrated *in vacuo* and the residue was chromatographed on silica gel with 4% MeOH-CH_2Cl_2 to give 0.39 g of **166**: MS (ESI+) m/z 863.5 ($M+H^+$), 885.5 ($M+Na^+$); MS (ESI-) m/z 897.5 (M+Cl).

Step 5:

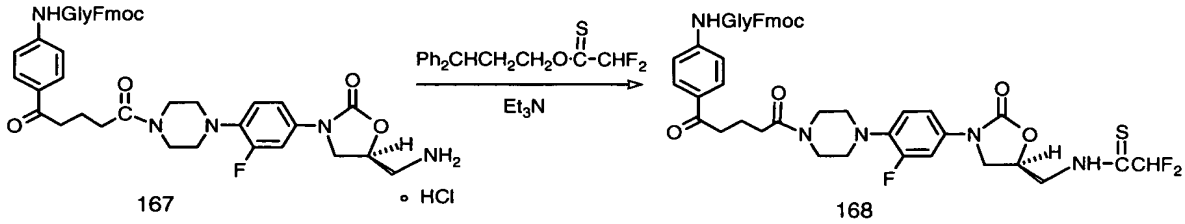


166 167

The product **166** from the previous reaction was cooled in an ice bath, under nitrogen, and, with stirring, treated dropwise during 1.5 min with 4N HCl in dioxane (3 ml). It

was kept in the ice bath for 45 min and at ambient temperature for 130 min. Excess hydrogen chloride was then removed under a stream of nitrogen and the resulting mixture was concentrated *in vacuo* to give 0.30 g of **167**.

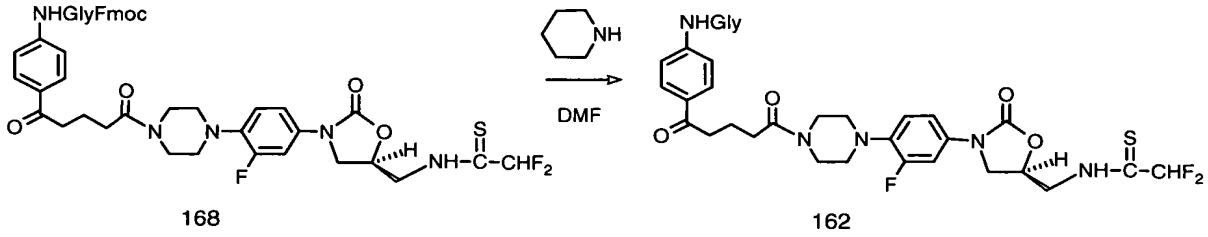
Step 6:



167 168

A stirred mixture of **167** (0.30 g) from the previous reaction in CH_2Cl_2 (25 ml), under nitrogen, was treated with triethylamine (0.11 ml) and then dropwise with a solution of O-(3,3-diphenylpropyl) difluoroethanethioate (0.15 g, 0.49 mmol) in CH_2Cl_2 (2 ml). It was kept at ambient temperature and treated with additional portions of O-(3,3-diphenylpropyl) difluoroethanethioate (0.05 g in 1 ml of CH_2Cl_2) after 2 h and 4 h. The resulting mixture was kept at ambient temperature for 18 h and concentrated *in vacuo*. The residue was triturated with 3% MeOH-CH_2Cl_2 and the resulting solid was crystallized from CH_2Cl_2-Et_2O to give 0.29 g of **168**: MS (ESI+) m/z 879.6 ($M+Na^+$); MS (ESI-) m/z 855.3 (M-H), 891.2 (M+Cl).

Step 7:



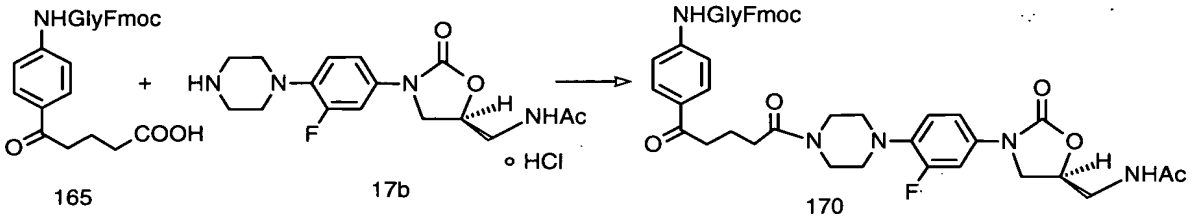
168 162

A stirred mixture of **168** (0.29 g) from the previous reaction in DMF (2 ml), under nitrogen, was treated dropwise with piperidine (0.07 ml), kept at ambient temperature for 30 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 4% MeOH-0.2% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH gave 0.08 g of **162**: mp 196-197°C (dec); ^1H NMR [400 MHz, $(CD_3)_2SO$] δ 1.85 (m, 2H), 2.43 (t, 2H), 292, 2.96 (m, m, 4H), 3.03 (t, 2H), 3.35 (s, 3H), 3.60 (m, 4H), 3.82

(dd, 1H), 3.94 (m, 2H), 4.15 (t, 1H), 5.00 (m, 1H), 6.32, 6.46, 6.59 (s, s, s, 1H), 7.07 (t, 1H), 7.19 (dd, 1H), 7.51 (d, 1H), 7.77 (d, 2H), 7.95 (d, 2H); MS (ESI+) m/z 635.4 ($M+H^+$); MS (ESI-) m/z 633.3 (M-H), 669.3 (M+Cl); IR (drift) 3394, 3258, 1743, 1693, 1672, 1645 cm^{-1}. Anal. calcd for $C_{29}H_{33}F_3N_6O_5S$; C, 54.88; H, 5.24; N, 13.24. Found: C, 54.46; H, 5.27; N, 13.09.

Example 59: N^1-(4-{5-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopentanoyl}phenyl)glycinamide 169.

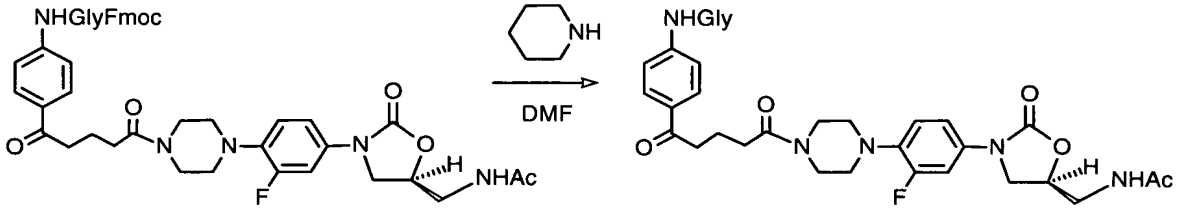
Step 1:



165 17b 170

A stirred mixture of **165** (0.486 g, 0.999 mmol) and **17b** (0.4 g, 1.1 mmol) in pyridine (8 ml), under nitrogen, was treated with EDC (0.25 g, 1.3 mmol) and DMAP (10 mg), kept at ambient temperature for 24 h and concentrated *in vacuo*. A mixture of the residue in water was extracted with CH_2Cl_2; the extract was washed with saturated $NaHCO_3$ and brine and concentrated to give 0.6 g of **170**, a yellow solid: MS (ESI-) m/z 839.4 (M+Cl).

Step 2:



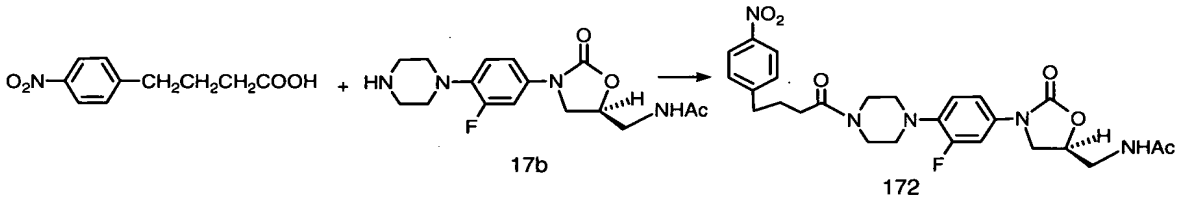
170 169

A stirred suspension of **170** (0.6 g, 0.75 mmol) in DMF (5 ml), under nitrogen, was treated with piperidine (0.15 ml), kept at ambient temperature for 30 min and concentrated *in vacuo*. Chromatography of the solid residue on silica gel with 4% MeOH-0.2% NH_4OH-CH_2Cl_2 to 10% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH gave 0.24 g, mp 189-190°C and 0.06 g, mp

178-181°C of **169**: ^{1}H NMR [400 MHz, $(CD_3)_2SO$]δ 1.83 (s, 3H), 1.84 (m, 2H), 2.42 (t, 2H), 2.91, 2.95 (m, m, 4H), 3.03 (t, 2H), 3.31 (s, 2H), 3.35 (s), 3.40 (t, 2H), 3.60 (m, 4H), 3.70 (dd, 1H), 4.08 (t, 1h), 4.71 (m, 1H), 7.06 (t, 1H), 7.18 (dd, 1H), 7.50 (dd, 1H), 7.78 (d, 2H), 7.95 (d, 2H), 8.26 (t, 1H); IR (drift) 3336, 3258, 1725, 1678, 1651, 1631 cm^{-1}; MS (ESI+) m/z 583.3 ($M+H^+$); MS (ESI-) m/z 617.3 (M+Cl). Anal. calcd for $C_{29}H_{35}FN_6O_6$: C, 59.78; H, 6.05; N, 14.42. Found: C, 59.14; H, 6.10; N, 14.22.

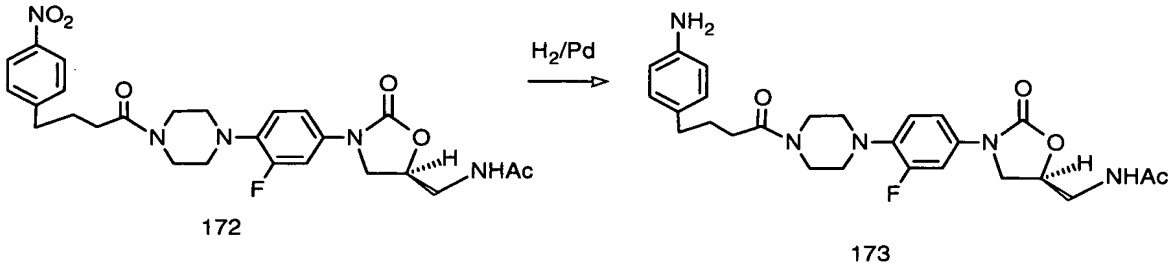
Example 60: N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-1-piperazinyl]-4-oxobutyl}phenyl)-2-aminoacetamide 171.

Step 1:



A stirred mixture of 4-(4-nitrophenyl)butanoic acid (0.9 g, 4.3 mmol) and triethylamine (0.69 ml) in THF (20 ml), under nitrogen, was cooled in an ice-MeOH bath and treated, dropwise during 15 min, with isobutyl chloroformate (0.66 ml). It was kept in the bath for 50 min and the resulting thick suspension was treated with a mixture of **17b** (1.44 g, 4.28 mmol), triethylamine (0.69 ml) and THF (20 ml). This mixture was kept in the ice-MeOH bath for 3 h and then mixed with EtOAc to give a mixture which contained solid product. It was washed with saturated $NaHCO_3$ and water and filtered to give 1.11 g of **172**. The organic solution was concentrated to about 50 ml to give 0.94 g of additional product (**26**): MS (ESI) m/z 550.4 ($M+Na^+$).

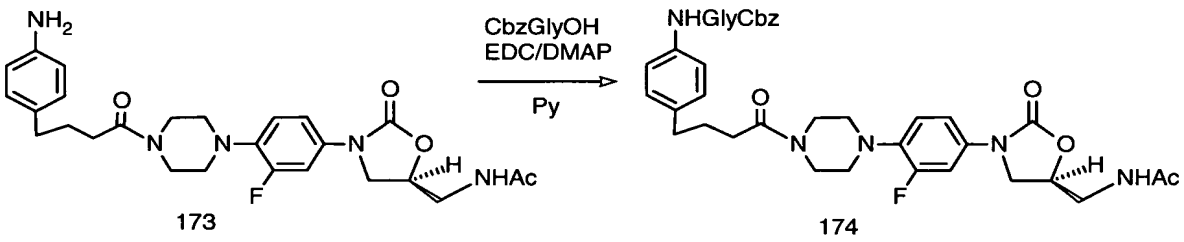
Step 2:



172 173

A mixture of 172 (1.1 g, 2.08 mmol), CH_2Cl_2 (75 ml), MeOH (75 ml) and 10% palladium-on-carbon catalyst (0.65 g) was hydrogenated for 90 min at an initial pressure of 19 psi which was raised to 50 psi during 35 min. The catalyst was removed by filtration through celite, the solid was washed with 50% MeOH-CH_2Cl_2, and the filtrate was concentrated to give 0.74 g of product. A sample of this material was chromatographed on silica gel with 5% MeOH-$CHCl_3$ and crystallized from MeOH-EtOAc to give 173: mp 141-143°C (dec); MS (ESI) m/z 498.4 ($M+H^+$), 520.4 ($M+Na^+$); IR (drift) 3340, 3302, 3231, 1733, 1645, 1628 cm^{-1}. Anal. calcd for $C_{26}H_{32}FN_5O_4$: C, 62.76; H, 6.48; N, 14.07. Found: C, 62.29; H, 6.50; N, 13.85.

Step 3:

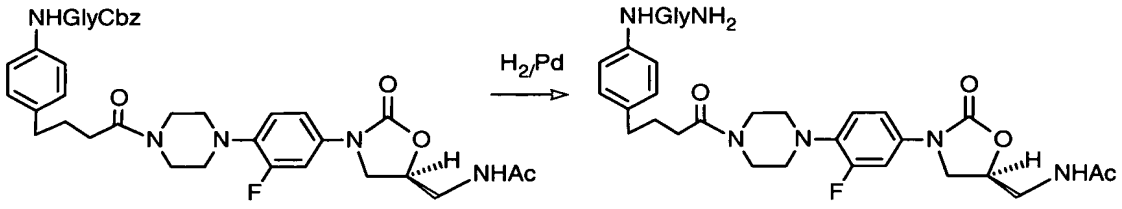


173 174

A stirred mixture of N-carbobenzyloxyglycine (0.19 g, 0.91 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.19 g, 0.99 mmol) and pyridine (5 ml), under nitrogen, was treated with 173 (0.43 g, 0.86 mmol) and 4-dimethylaminopyridine (DMAP, 10 mg) and kept at ambient temperature for 6 h. By TLC (0.5% NH_4OH-7.5% MeOH-CH_2Cl_2) there had been little reaction. Additional Cbz glycine (0.19 g) and EDC (0.19 g) were added and the mixture was kept at ambient temperature for 18 h. By TLC with the solvent system that contained ammonium hydroxide there still had been no reaction but TLC with 10% MeOH-CH_2Cl_2 demonstrated that the reaction was complete. The mixture was concentrated *in vacuo* and the residue was mixed with CH_2Cl_2 and 1N HCl to give a mixture which contained solid product. It was extracted with CH_2Cl_2 and filtered to give 0.37 g of product. The extract was washed with water and brine and concentrated. The residue

was chromatographed on silica gel with 7.5% MeOH-$CHCl_3$ to give 0.20 g of additional product **174**: MS (ESI) m/z 689.5 ($M+H^+$), 711.4 ($M+Na^+$).

Step 4:

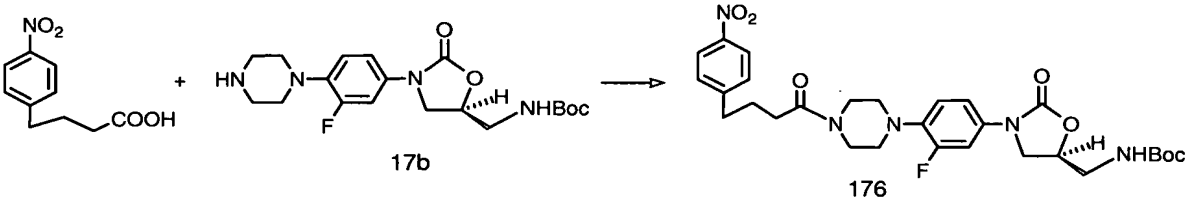


174 171

A mixture of **174** (0.53 g, 0.77 mmol), MeOH (90 ml), CH_2Cl_2 (60 ml) and 10% palladium-on-carbon catalyst (0.28 g) was hydrogenated at an initial pressure of 36 psi for 7 h and filtered through celite. The solid was washed with 60% MeOH-CH_2Cl_2 and the filtrate was concentrated. Chromatography of the residue on silica gel with 0.5% NH_4OH-10% MeOH-$CHCl_3$ and crystallization of the product from MeOH gave 0.199 g of **171**: mp 199-200°C (dec); MS (ESI) m/z 555.4 ($M+H^+$); IR (drift) 3302, 1732, 1653, 1628 cm^{-1}. Anal. calcd for $C_{28}H_{35}FN_6O_5$: C, 60.64; H, 6.38; N, 15.15. Found: C, 60.59; H, 6.46; N, 15.07.

Example 61: 2-Amino-N-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutyl}phenyl)acetamide 175.

Step 1:

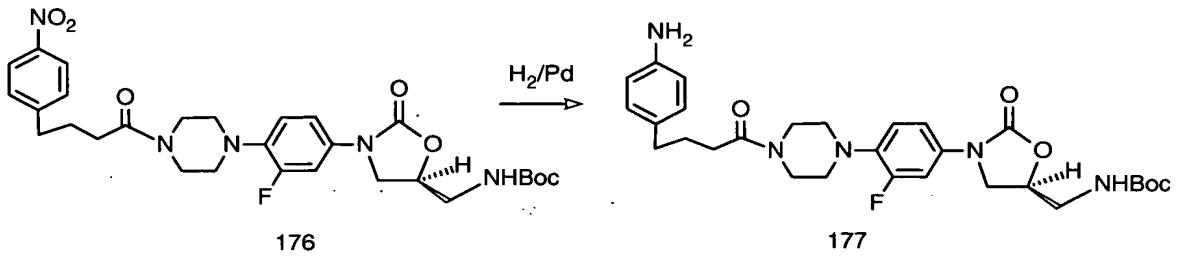


17b 176

A stirred mixture of 4-(4-nitrophenyl)butanoic acid (0.9 g, 4.3 mmol), triethylamine (0.69 ml) and THF (20 ml), under nitrogen, was cooled in an ice-MeOH bath and treated, dropwise during 30 sec, with isobutyl chloroformate (0.66 ml). It was kept in the bath for 50 min and then treated, portionwise during 5 min, with a mixture of **17b**

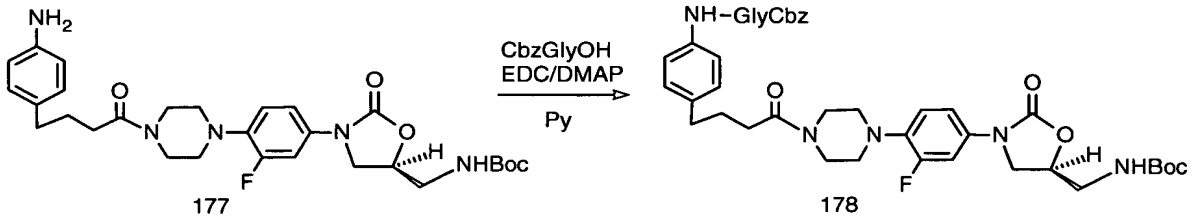
(1.69 g, 4.28 mmol), triethylamine (0.69 ml) and THF (13 ml). This mixture was kept in the ice-methanol bath for 90 min when it was concentrated *in vacuo*. A mixture of the residue in CH_2Cl_2 was washed with saturated $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated to give 2.54 g of **176**: MS (ESI) m/z 586.5 ($M+H^+$), 608.4 ($M+Na^+$).

Step 2:



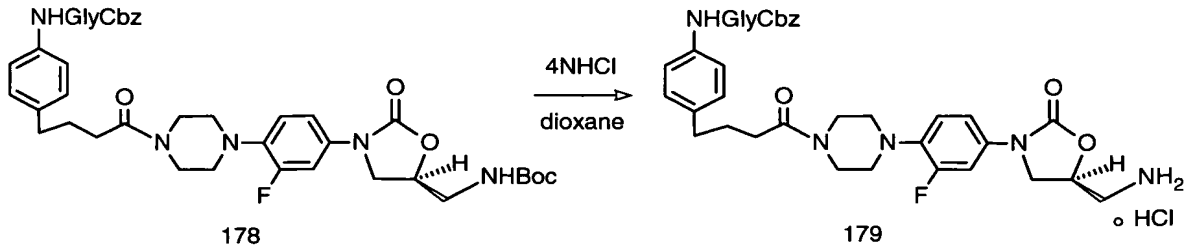
A mixture of **176** (1.25 g, 2.13 mmol), 10% palladium-on-carbon catalyst (0.7 g), MeOH (75 ml) and CH_2Cl_2 (75 ml) was hydrogenated at an initial pressure of 50 psi for 80 min and filtered through celite. The solid was washed with 50% MeOH-CH_2Cl_2 and the filtrate was concentrated *in vacuo* to give 1.17 g of **177**: MS (ESI) m/z 556.5 ($M+H^+$), 578.5 ($M+Na^+$), 594.5 ($M+K^+$).

Step 3:



A stirred mixture of N-Cbz glycine (0.50 g, 2.39 mmol) and EDC (0.46, 2.4 mmol) in pyridine (15 ml), under nitrogen, was kept at ambient temperature for 10 min and treated with **177** (0.97 g, 1.75 mmol) and DMAP (15 mg). It was kept at ambient temperature for 22 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2-4% MeOH-CH_2Cl_2 gave 0.73 g (56%) of **178**: MS (ESI) m/z 747.6 ($M+H^+$), 769.5 ($M+Na^+$).

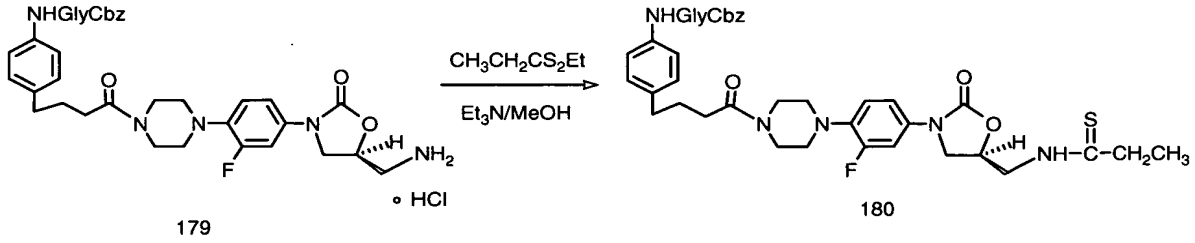
Step 4:



178 179

A stirred suspension of **178** (0.5 g, 0.67 mmol) in dioxane (10 ml) was treated, dropwise during 4 min, with ice-cold 4N HCl in dioxane (5 ml). The mixture was cooled in an ice bath during the addition and kept in the bath for 1 h, at ambient temperature for 2 h and at 4°C for 18 h. It was then concentrated *in vacuo* to give 0.50 g of **179**: MS (ESI) m/z 647.6 ($M+H^+$).

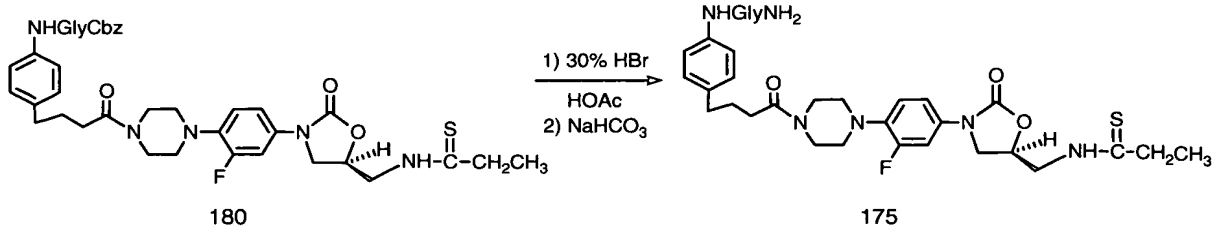
Step 5:



179 180

A stirred suspension of **179** (0.50 g) in MeOH (20 ml), under nitrogen, was treated with triethylamine (0.37 ml, 2.66 mmol) and ethyl dithiopropionate (0.13 ml, 1.0 mmol) and kept at ambient temperature for 22 h. It was then concentrated under a stream of nitrogen for 30 min and filtered. The solid was washed with cold MeOH and dried to give 0.30 g of **180**: MS (ESI) m/z 719.6 ($M+H^+$), 741.6 ($M+Na^+$).

Step 6:



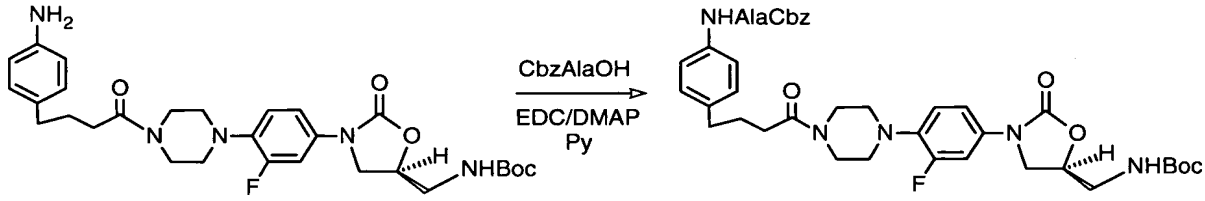
180 175

Solid **180** (0.28 g, 0.39 mmol) was mixed with 30% hydrogen bromide in acetic acid (3.9 ml) and stirred at ambient temperature for 30 min. The resulting solution was

diluted with Et_2O (50 ml) and the liquid was decanted from the solid. This was repeated twice and the solid was then collected by filtration, washed with Et_2O, dissolved in water and made alkaline with saturated $NaHCO_3$. The resulting solid was collected by filtration, washed with water and dried to give 0.18 g of crude product. Additional product (0.01 g) was obtained by extracting the aqueous filtrate with CH_2Cl_2. Chromatography of the combined product on silica gel with 0.4% NH_4OH-8% MeOH-$CHCl_3$ and crystallization from EtOAc-MeOH gave 0.0688 g of **175**: mp 161-163°C (dec) with softening at 148°C; MS (ESI) m/z 585.5 ($M+H^+$), 607.4 ($M+Na^+$); IR (drift) 3322, 3256, 1753, 1749, 1744, 1727, 1681, 1631 cm^{-1}. Anal. calcd for $C_{29}H_{37}FN_6O_4S$: C, 59.57; H, 6.38; N, 14.37. Found: C, 58.19; H, 6.48; N, 13.85.

Example 62: (*S*)-2-Amino-N-(4-{4-[4-(2-fluoro-4-{(5*S*)-2-oxo-5-[(propanethiolylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-1-piperazinyl]-4-oxobutyl}phenyl)propanamide 181.

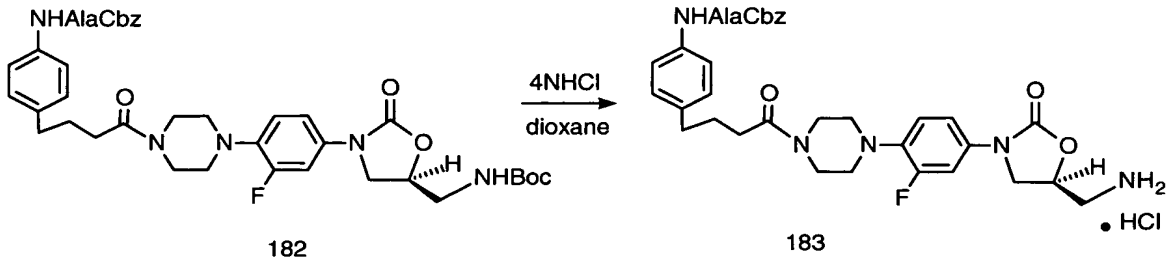
Step 1:



177 182

A stirred mixture of N-carbobenzyloxy-L-alanine (0.47 g, 2.1 mmol) and EDC (0.43 g, 2.2 mmol) in pyridine (15 ml), under nitrogen, was treated with **177** (0.91 g, 1.64 mmol) and DMAP (15 mg), kept at ambient temperature for 20 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2-4% MeOH-$CHCl_3$ gave 0.70 g of **182**: MS (ESI) m/z 783.7 ($M+Na^+$).

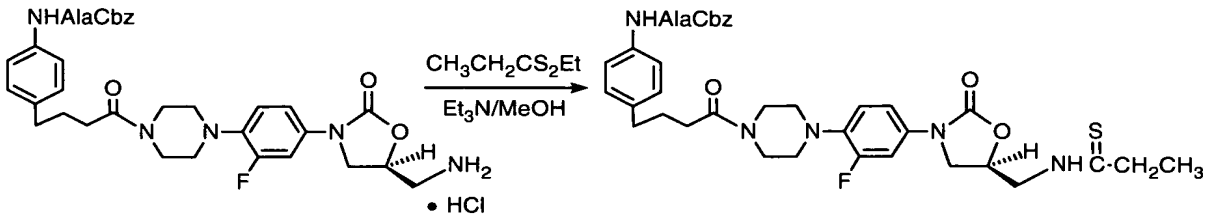
Step 2:



182 183

A stirred solution of **182** (0.57 g, 0.75 mmol) in dioxane (14 ml), under nitrogen, was treated, dropwise during 2.5 min, with ice cold 4N hydrogen chloride in dioxane (7.5 ml). The mixture was cooled in an ice bath during the addition and kept in the bath for 90 min, at ambient temperature for 4 h and at 4°C for 16 h. Hydrogen chloride was removed under a stream of nitrogen and the resulting mixture was concentrated *in vacuo* to give **183**, a white solid.

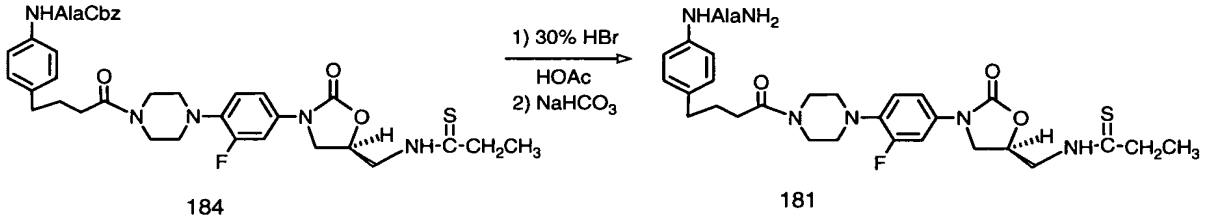
Step 3:



183 184

A stirred mixture of **183** from the previous reaction and triethylamine (0.37 ml) in MeOH (20 ml), under nitrogen, was treated with ethyl dithiopropionate (0.13 ml), kept at ambient temperature for 72 h and concentrated. Chromatography of the residue on silica gel with 2-3% MeOH-$CHCl_3$ gave 0.42 g of **184**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 1.12 (t, 3H), 1.26 (d, 3H), 1.77 (m, 2H), 2.32 (t, 2H), 2.55 (m, 4H), 2.90 (m, 4H), 3.56 (m, 4H), 3.78 (dd, 1H), 3.89 (t, 2H), 4.13 (m, 2H), 4.94 (m, 1H), 5.01 (s, 2H), 7.05 (t, 1H), 7.13 (m, 3H), 7.33 (m, 5H), 7.47 (m, 3H), 7.57 (d, 1H), 9.91 (s, 1H), 10.31 (t, 1H); MS (ESI) m/z 733.5 ($M+H^+$), 755.5 ($M+Na^+$).

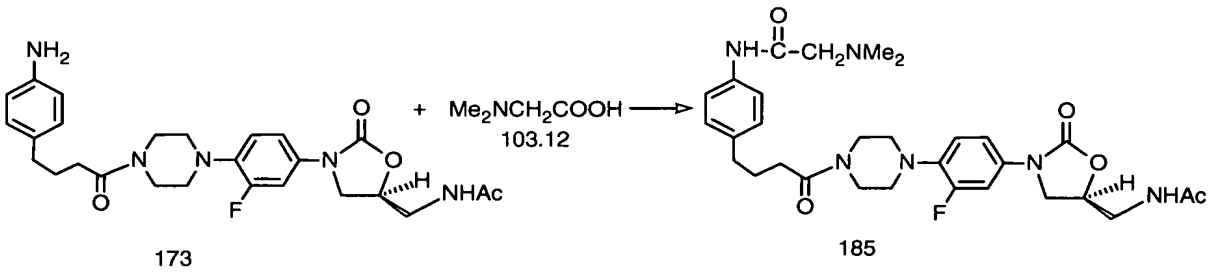
Step 4:



184 181

A mixture of **184** (0.40 g, 0.55 mmol) and 30% hydrogen bromide in acetic acid (5.0 ml) was stirred for 35 min at ambient temperature and then diluted with Et_2O (100 ml). The liquid was decanted from the resulting solid which was washed twice with Et_2O, collected by filtration and washed with Et_2O. The solid was dissolved in water (20 ml) and neutralized (pH 9-10) with saturated $NaHCO_3$ to give a solid which was collected by filtration, dried and chromatographed on silica gel with 0.2% NH_4OH-4% MeOH-$CHCl_3$. The product was crystallized from MeOH to give 0.24 g of **181**: MS (ESI) m/z 599.3 ($M+H^+$); IR (drift) 3263, 1753, 1751, 1744, 1727, 1676, 1662, 1645, 1639, 1633 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{40}FN_6O_4S$ ($M+H^+$) 599.2816, found 599.2824. Anal. calcd for $C_{30}H_{39}FN_6O_4S \circ 0.5\ H_2O$: C, 59.29; H, 6.63; N, 13.83. Found: C, 59.10; H, 6.79; N, 13.59.

Example 63: N-(4-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutyl)phenyl)-2-(dimethylamino)acetamide 185.



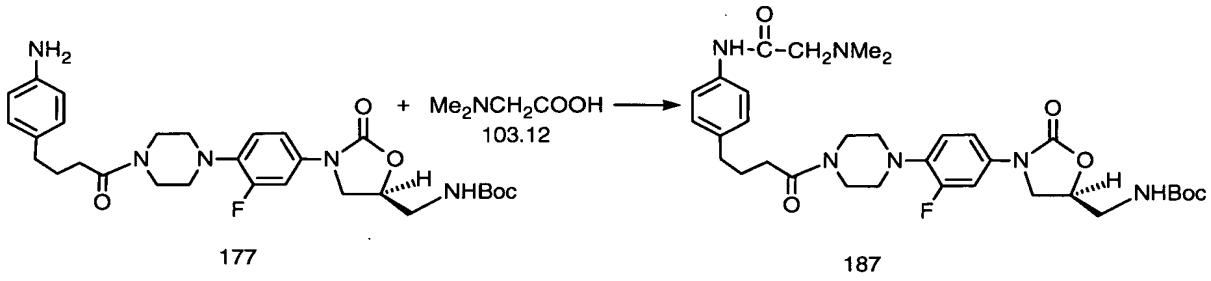
173 185

A stirred mixture of N,N-dimethylglycine (0.0263 g, 0.255 mmol) in pyridine (4 ml), under nitrogen, was treated with EDC (0.049 g), DMAP (5 mg) and **173** (0.127 g, 0.255 mmol), kept at ambient temperature for 3 h 10 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2-6% MeOH-CH_2Cl_2 gave the

product which was dissolved in CH_2Cl_2 and concentrated to give **185**, a foam: MS (ESI+) m/z 583.5 ($M+H^+$), 605.4 ($M+Na^+$); MS (ESI-) m/z 581.4 (M-H), 617.4 (M+Cl); IR (drift) 3287, 1743, 1676, 1645 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{40}FN_6O_5$ ($M+H^+$) 583.3044, found 583.3058.

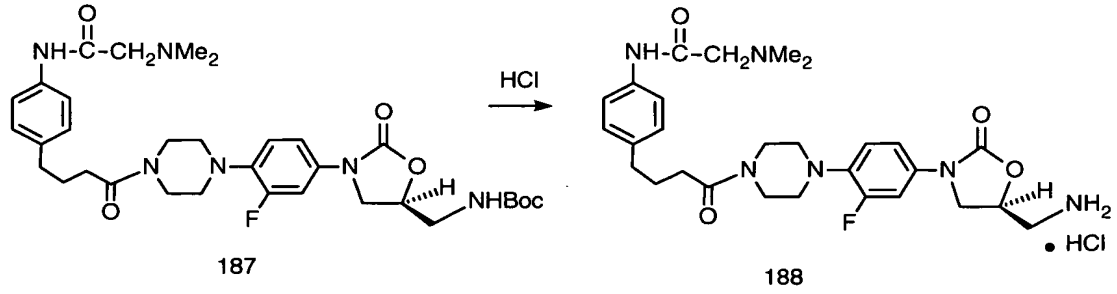
Example 64: N-(4-{4-[4-(4-{(5*S*)-5-[(Ethanethiolylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutyl}phenyl)-2-(dimethylamino)acetamide 186.

Step 1:



A stirred mixture of N,N-dimethylglycine (0.028 g, 0.27 mmol) in pyridine (4 ml), under nitrogen was treated with EDC (0.052 g, 0.27 mmol), DMAP (5 mg) and **177** (0.15 g, 0.27 mmol), kept at ambient temperature for 5 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2-3% MeOH-CH_2Cl_2 gave 0.09 g of **187**: MS (ESI+) m/z 641.5 ($M+H^+$); MS (ESI-) m/z 639.4 (M-H), 675.4 (M+Cl).

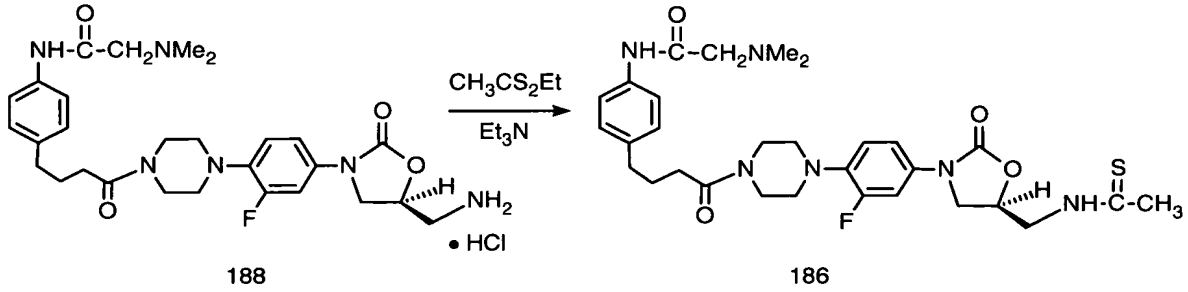
Step 2:



Compound **187** (0.21 g, 0.33 mmol) was cooled in an ice bath, under nitrogen and treated, dropwise with 4N HCl in dioxane (3.0 ml). The mixture was kept in the ice bath for 1 h and at ambient temperature for 30 min with occasional swirling. It was

placed under a stream of nitrogen for 30 min and then concentrated *in vacuo* to give **188**, a white powder: MS (ESI+) m/z 541.4 ($M+H^+$); MS (ESI-) m/z 575.4 (M+Cl).

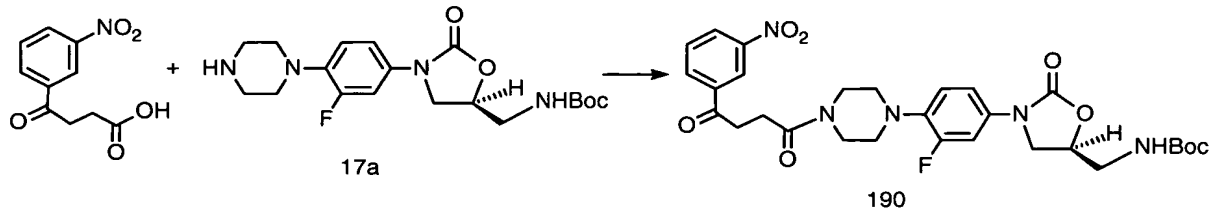
Step 3:



A stirred mixture of **188** from the previous reaction and MeOH (2.5 ml), under nitrogen was treated with triethylamine (0.4 ml) and ethyl dithioacetate (0.088 ml), kept at ambient temperature for 1 h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2.5-4% MeOH-CH_2Cl_2 gave 0.13 g of **186**: MS (ESI+) m/z 599.4 ($M+H^+$); MS (ESI-) m/z 597.3 (M-H), 633.3 (M+Cl); IR (drift) 3251, 1754, 1680, 1663, 1645, 1638 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{40}FN_6O_4S$ ($M+H^+$) 599.2816, found 599.2827.

Example 65: N^1-(3-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-1-hydroxy-4-oxobutyl}phenyl)glycinamide 189.

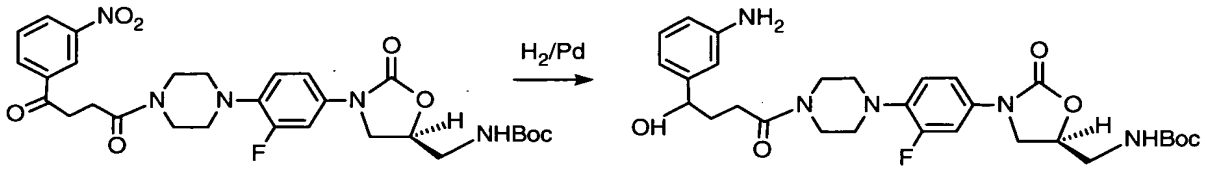
Step 1:



A stirred mixture of 3-nitro-□-oxo-benzenebutanoic acid,[13] (0.9 g, 4.1 mmol) and pyridine (20 ml), under nitrogen was treated with EDC (0.96 g, 5.0 mmol), kept at ambient temperature for 2 min and treated with **17a** (1.69 g, 4.29 mmol) and DMAP (20 mg). It was kept at ambient temperature for 46 h and concentrated *in vacuo*. A solution of the residue in CH_2Cl_2 was washed with dilute $KHSO_4$ and water and

concentrated *in vacuo*. Chromatography of the residue on silica gel with 1 to 2% MeOH-CH_2Cl_2 gave 2.2 g of **190**. A sample was recrystallized from EtOAc-hexane: mp 124-126°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.90 (t, 2H), 3.04, 3.13 (m, m, 4H), 3.39 (t, 2H), 3.52 (m, 2H), 3.79 (m, 5H), 4.00 (t, 1H), 4.75 (m, 1H), 4.96 (m, 1H), 6.98 (t, 1H), 7.09 (dd, 1H), 7.49 (dd, 1H), 7.69 (t, 1H), 8.35 (d, 1H), 8.43 (d, 1H), 8.86 (m, 1H); MS (ESI+) m/z 599.8 ($M+H^+$), 621.8 ($M+Na^+$); MS (ESI-) m/z 597.8 (M-H), 633.7 (M+Cl).

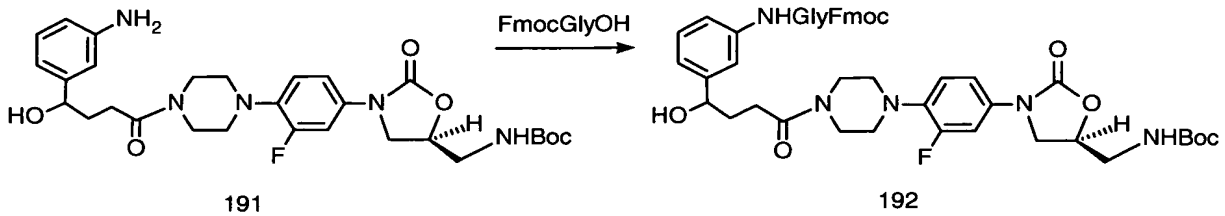
Step 2:



190 191

A mixture of **190** (0.4 g, 0.67 mmol), MeOH (35 ml), CH_2Cl_2 (35 ml) and 10% palladium-on-carbon catalyst (0.2 g) was hydrogenated at an initial pressure of 29 psi for 25 min. Complete reduction of the ketone and nitro groups with little of the over reduced, deshydroxy material was obtained. The mixture was filtered through celite and the filtrate was concentrated. Chromatography of the residue over silica gel with 2 to 4% MeOH-CH_2Cl_2 gave 0.26 g of **1912**: MS (ESI+) m/z 572.4 ($M+H^+$), 594.4 ($M+Na^+$); MS (ESI-) m/z 570.3 (M-H), 606.3 (M+Cl).

Step 3:

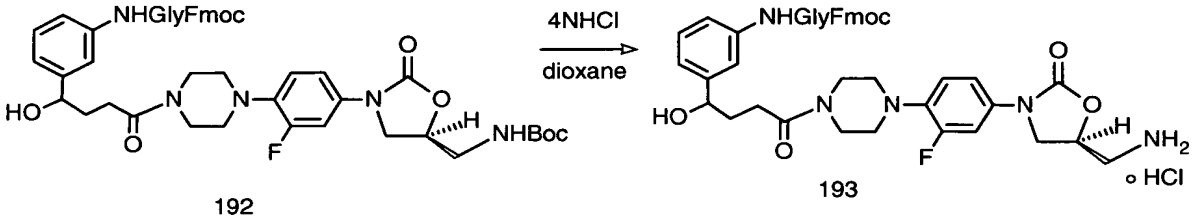


191 192

A stirred mixture of N-Fmoc glycine (0.45 g, 1.5 mmol) and DMF (8 ml), under nitrogen, was treated with HOBT (0.254 g) and 0.5 M DCC in CH_2Cl_2 (4.65 ml), kept at ambient temperature for 50 min and treated, dropwise, with a solution of **191**(0.88

g, 1.5 mmol) in DMF (2 ml). It was kept at ambient temperature for 90 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2.5% MeOH-CH_2Cl_2 gave 0.63 g of **192**: MS (ESI+) m/z 851.5 ($M+H^+$), 873.5 ($M+Na^+$).

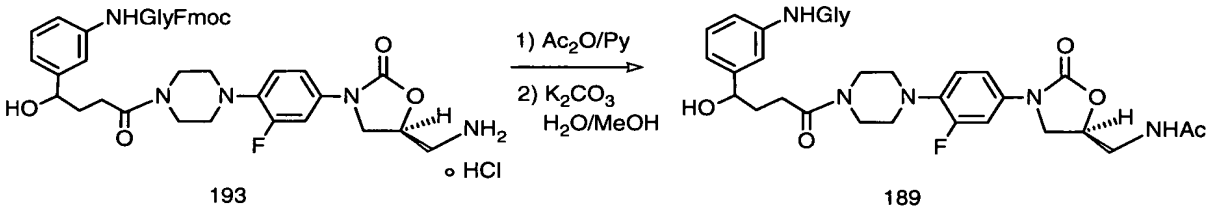
Step 4:



192 193

Ice cold 4N hydrogen chloride in dioxane (4.5 ml) was added, dropwise under nitrogen, to **192** (0.65 g, 0.765 mmol) which had been cooled in an ice bath. The mixture was kept in the ice bath for 30 min and at ambient temperature for 90 min. It was then placed under a stream of nitrogen for 10 min and concentrated *in vacuo* to give **193**, a white solid: MS (ESI+) m/z 751.5 ($M+H^+$); MS (ESI-) m/z 785.2 (M+Cl).

Step 5:



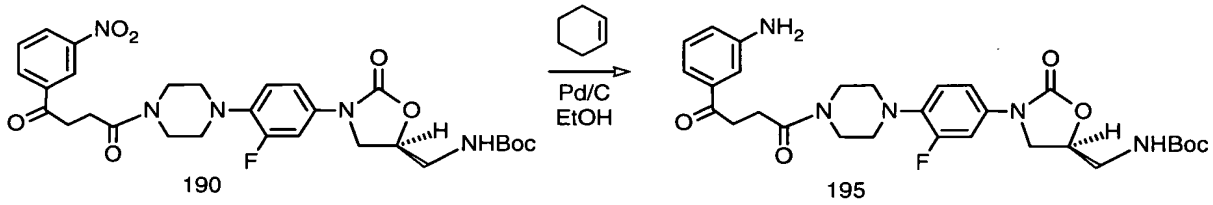
193 189

An ice cold, stirred mixture of the product **193** from the previous reaction in pyridine (5 ml), under nitrogen, was treated, dropwise with a solution of acetic anhydride (1.25 ml) in pyridine (1.5 ml). It was kept in the ice bath for 40 min and at ambient temperature for 50 min and then concentrated *in vacuo*. A mixture of the residue in CH_2Cl_2 was washed with saturated $NaHCO_3$, water and brine. Concentration of the CH_2Cl_2 solution gave 0.78 g of a mixture of mono and diacylated products. A stirred mixture of this material (0.53 g) in MeOH (15 ml), under nitrogen was treated with 10% aqueous K_2CO_3 (1.8 ml) and kept at ambient temperature for 18 h. It was concentrated *in vacuo*. Chromatography of the residue on silica gel with 12% MeOH-0.6% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH gave 0.102 g of **189**: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.81 (s, 3H), 1.81 (m, 2H), 2.37 (t, 2H), 2.88

(m, 4H), 3.23 (s, 2H), 3.32 (broad s, 3H), 3.38 (t, 2H), 3.54 (m, 4H), 3.68 (dd, 1H), 4.06 (t, 1H), 4.52 (m, 1H), 4.69 (m, 1H), 5.26 (d, 1H), 6.98-7.25 (m, 4H), 7.45-7.56 (m, 3H), 8.23 (t, 1H); MS (ESI+) m/z 571.3 ($M+H^+$), 593.3 ($M+Na^+$); MS (ESI-) m/z 569.1 (M-H), 605.1 (M+Cl); IR (drift) 3444, 3372, 3342, 3307, 1749, 1680, 1663 cm^{-1}. Anal. calcd for $C_{28}H_{35}FN_6O_6 \circ 2H_2O$: C, 55.44; H, 6.48; N, 13.85. Found: C, 54.84; H, 6.48; N, 13.60.

Example 66: N^1-[3-(4-{4-[4-((5*S*)-5-{[(2,2-Difluoroethanethiolyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]piperazin-1-yl}-4-oxobutanoyl)phenyl]glycinamide 194.

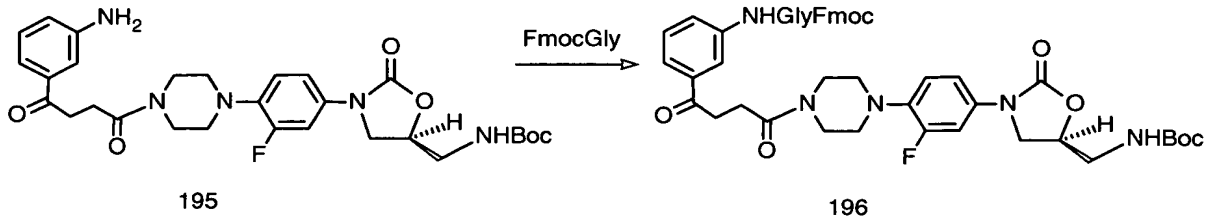
Step1:



190 195

A stirred mixture of **190** (2.1 g, 3.5 mmol), cyclohexene (4 ml), 10% palladium-on-carbon catalyst (0.5 g) and EtOH (50 ml) was refluxed, under nitrogen for 2.5 h, kept at ambient temperature for 20 h, refluxed for 4 h and kept at ambient temperature for 3 d. It was then diluted with CH_2Cl_2 and filtered through celite. The solid was washed with 10% EtOAc-CH_2Cl_2 and the combined filtrate was concentrated *in vacuo*. Chromatography of the residue on silica gel with 3% MeOH-CH_2Cl_2 gave **195**: MS (ESI+) m/z 570.4 (M+H), 592.4 ($M+Na^+$).

Step 2:

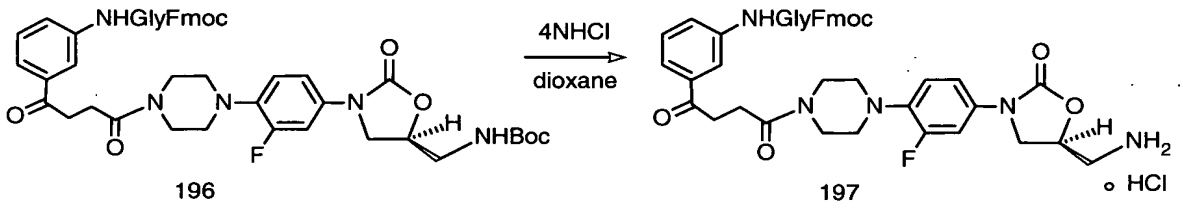


195 196

A stirred mixture of N-Fmoc glycine (0.155 g, 0.521 mmol), HOBT (0.09 g) and DMF (3 ml) was treated, dropwise during 1.5 min, with 0.5 M DCC in CH_2Cl_2 (1.6

ml) and kept at ambient temperature for 50 min. It was then treated, dropwise during 2 min, with a solution of **195** (0.30 g, 0.53 mmol) in DMF (2 ml) and kept at ambient temperature for 20 h. The mixture was concentrated *in vacuo* and the residue was mixed with water to give a solid which was collected by filtration, washed with water and dried *in vacuo*. Chromatography of this material on silica gel with 7.5% MeOH-CH_2Cl_2 gave 0.42 g of **196**: MS (ESI+) m/z 849.4 ($M+H^+$), 871.4 ($M+Na^+$); MS (ESI-) m/z 847.3 (M-H), 883.2 ($M+Cl^-$).

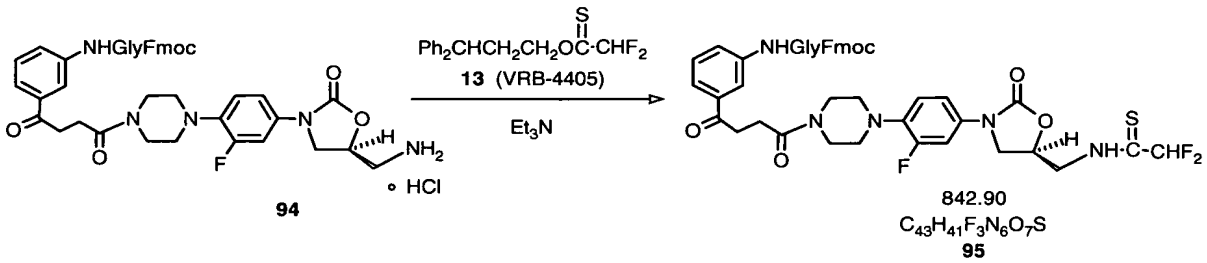
Step 3:



196 197

Ice cold **196** (0.74 g, 0.87 mmol), under nitrogen, was treated, dropwise with ice cold 4N HCl in dioxane (6.2 ml) and the mixture was stirred in the ice bath for 30 min and at ambient temperature for 90 min. It was concentrated to give 0.72 g of **197**: MS (ESI+) m/z 749.4 ($M+H^+$); MS (ESI-) m/z 783.2 (M+Cl).

Step 4:

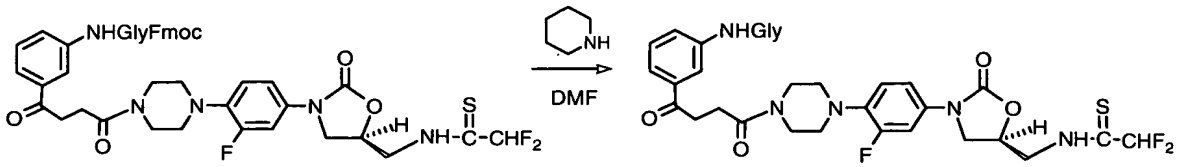


94

842.90
$C_{43}H_{41}F_3N_6O_7S$
95

A stirred mixture of **197** (0.22 g) and triethylamine (0.08 ml) in CH_2Cl_2 (20 ml), under nitrogen, was treated, dropwise, with a solution of O-(3,3-diphenylpropyl) difluoroethanethioate (0.11 g, 0.36 mmol) in CH_2Cl_2 (0.5 ml) and kept at ambient temperature for 18 h. It was then concentrated *in vacuo* and the residue was chromatographed on silica gel with 3% MeOH-CH_2Cl_2 to give **198**: MS (ESI+) m/z 865.3 ($M+Na^+$); MS (ESI-) m/z 841.3 (M-H), 877.4 (M+Cl).

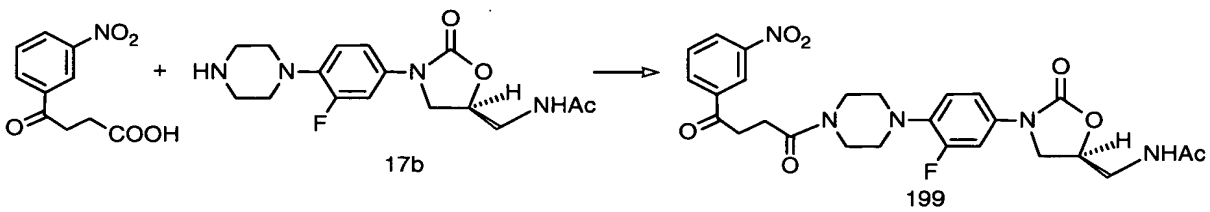
Step 5:



198 194

A stirred mixture of **198**, prepared from 0.49 g of **197**, in DMF (3 ml), under nitrogen, was treated with piperidine (0.10 ml), kept at ambient temperature for 40 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 7.5% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH-EtOAc gave 0.030 g of **194**: ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 2.76 (t, 2H), 2.92, 3.02 (s, s, 4H), 3.23 (t, 2H), 3.34 (broad s), 3.40 (s, 2H), 3.60, 3.69 (s, s, 4H), 3.84 (dd, 1H), 3.95 (m, 2H), 4.16 (t, 1H), 5.01 (m, 1H), 6.34, 6.48, 6.62 (s, s, s, 1H), 7.10 (t, 1H), 7.20 (dd, 1h), 7.48 (m, 2H), 7.70 (d, 1H), 7.89 (d, 1H), 8.25 (s, 1H); MS (ESI+) m/z 621.3 ($M+H^+$); MS (ESI-) m/z 619.3 (M-H). , 655.3 (M+Cl); IR (drift) 3268, 1753, 1691, 1685, 1682, 1645, 1638, 1636, 1628 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{32}F_3N_6O_5S$ ($M+H^+$) 621.2107, found 621.2117.

Example 67: N-{[(5*S*)-3-(3-Fluoro-4-{4-[4-(3-nitrophenyl)-4-oxobutanoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}actamide 199.



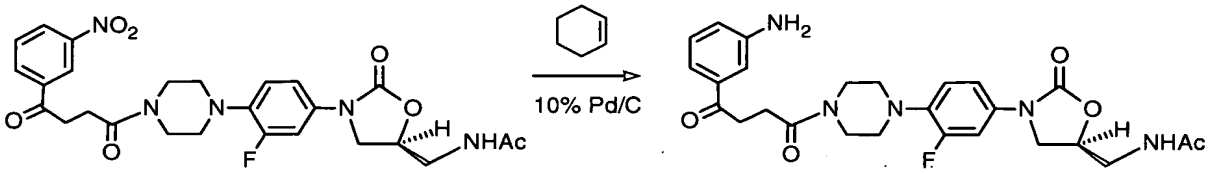
17b 199

A stirred mixture of 3-nitro-□-oxo-benzenebutanoic acid,[13] (0.9 g, 4.0 mmol) and triethylamine (0.69 ml) in THF (20 ml) was cooled, under nitrogen, in an MeOH-ice bath and treated, dropwise, with isobutyl chloroformate (0.66 ml). It was kept in the bath for 45 min and then treated, portionwise during 10 min, with a mixture of **17b**[12] (1.44 g, 4.28 mmol), triethylamine (0.69 ml) and THF. The mixture was kept in the bath for 2 h and at ambient temperature for 90 min and then concentrated *in vacuo*. Chromatography of the residue on silica gel with 2.5% MeOH-CH_2Cl_2 and crystallization of the product from CH_3CN gave 0.69 g of **199**: mp 178-179°C; IR (drift) 3280, 1736, 1691, 1672, 1650 cm^{-1}; MS (ESI+) m/z 541.8 ($M+H^+$), 563.8

(M+Na$^+$); MS (ESI-) m/z 540.8 (M-H), 575.8 (M+Cl). Anal. calcd for $C_{26}H_{28}FN_5O_7$: C, 57.67; H, 5.21; N, 12.93. Found: C, 57.86; H, 5.33; N, 12.84.

Example 68: N^1-(3-{4-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-4-oxobutanoyl}phenyl)glycinamide 200.

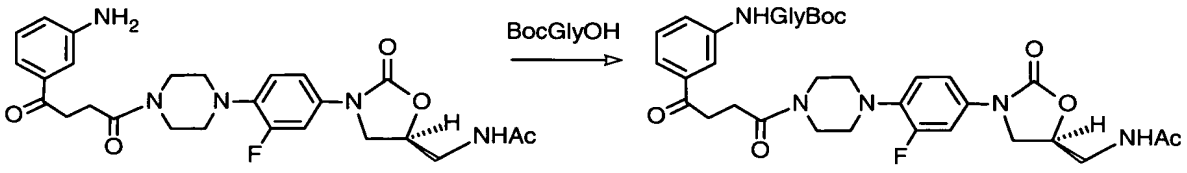
Step 1:



199 201

A stirred mixture of **199** (0.77 g, 1.42 mmol), cyclohexene (1.0 ml), 10% palladium-on-carbon catalyst (0.21 g) and EtOH (30 ml) was refluxed, under nitrogen for 1 h and kept at ambient temperature for 18 h. Additional catalyst (0.15 g) and cyclohexene (1 ml) were added and the mixture was refluxed for 3.5 h, cooled and filtered through celite. The solid was washed with EtOH and the filtrate was concentrated to give 0.26 g of recovered **199**. The solid was then washed with 50% MeOH-CH_2Cl_2 (300 ml); the filtrate was concentrated and the residue was chromatographed over silica gel with 2-4% MeOH-CH_2Cl_2. Trituration of the product with MeOH-CH_2Cl_2 gave 0.18 g of **201** as the hydrochloride salt: MS (ESI+) m/z 512.2 (M+H$^+$), 534.2 (M+Na$^+$); MS (ESI-) m/z 510.1 (M-H), 546.0 (M+Cl), 556.0 (M+HCO_2); IR (drift) several bands 3600-3400, 3355, 3281, 1738, 1682, 1662, 1632 cm^{-1}. Anal. calcd for $C_{26}H_{31}ClFN_5O_5$: C, 56.99; H, 5.70; N, 12.78. Found: C, 57.12; H, 6.00; N, 12.63.

Step 2:

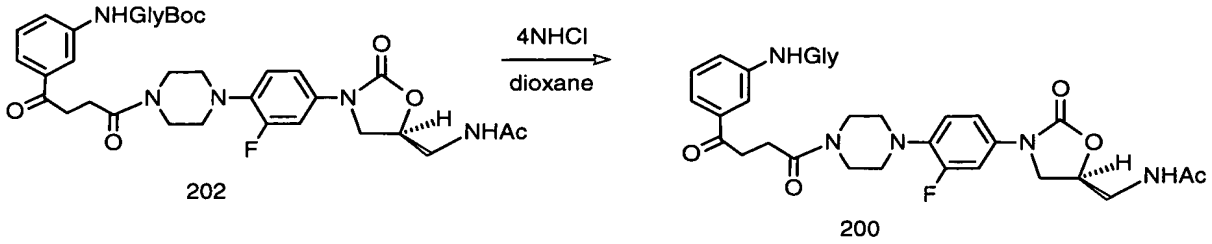


201 202

A stirred mixture of N-Boc glycine (0.052 g, 0.29 mmol), HOBT (0.05 g), 0.5 M dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 (0.9 ml) and DMF (4 ml) was kept at ambient temperature, under nitrogen, for 45 min and treated, dropwise, with a solution of **201** (0.15 g, 0.29 mmol) in DMF(2 ml). It was kept at ambient temperature for 22

h and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave 0.15 g of **202**: MS (ESI+) m/z 669.3 ($M+H^+$), 691.3 ($M+Na^+$); MS (ESI-) m/z 667.2 (M-H).

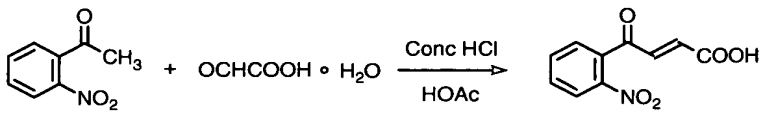
Step 3:



Ice cold 4N HCl in dioxane (1.3 ml) was added, dropwise with stirring under nitrogen, to ice cold **202** (0.15 g, 0.22 mmol). The mixture was kept in the ice bath for 1 h and at ambient temperature for 1 h and then concentrated under a stream of nitrogen to give a white solid. This was mixed with 5% aqueous $NaHCO_3$ and Et_2O to give a solid. Nitrogen was bubbled through the mixture to remove the Et_2O and the solid was collected by filtration and washed with cold water. The solid was triturated with hot MeOH and recrystallized from CH_2Cl_2-MeOH to give **200**: ^1H NMR [300 MHz, $(CH_3)_2SO$] δ 1.81 (s, 3H), 2.74 (t, 2H), 2.90, 3.00 (s, s, 4H), 3.15 (s, 1H), 3.20 (t, 2H), 3.28 (m, 4H), 3.38 (t, 2H), 3.58 (s, 2H), 3.66 (m, 3H), 4.07 (t, 1H), 4.69 (m, 1H), 7.07 (t, 1H), 7.16 (dd, 1H), 7.45 (m, 2H), 7.66 (d, 1H), 7.88 (d, 1H), 8.25 (m, 2H); IR (drift) 3316, 3287, 1748, 1702, 1682, 1662, 1630 cm^{-1}; HRMS (ESI+) calcd for $C_{28}H_{34}FN_6O_6$ ($M+H^+$) 569.2524, found 569.2510.

Example 69: N-{[(5*S*)-3-(4-{4-[4-(2-Aminophenyl)-4-oxobutanoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide 203.

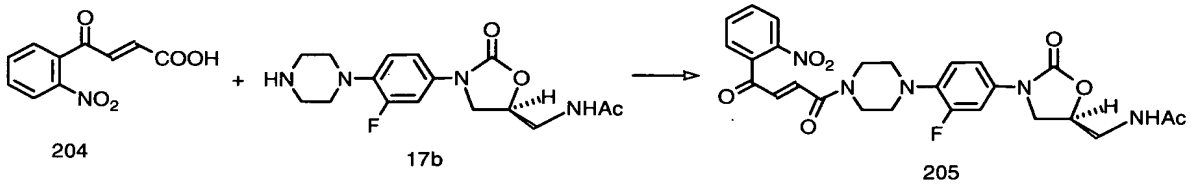
Step 1:



According to the method of Bianchi et.al. (*Eur. J. Med. Chem.* **1988**, *23*, 45-52) a stirred mixture of *o*-nitroacetophenone (2.48 g, 0.0150 mol), glyoxylic acid hydrate

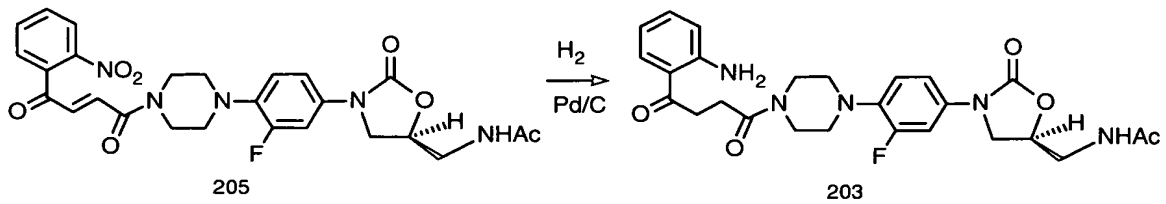
(1.53 g, 0.0166 mol) and acetic acid (25 ml) was treated with concentrated hydrochloric acid (2.5 ml) and warmed, under nitrogen at 125°C for 22 h. It was then concentrated *in vacuo* and the residue was mixed with ice and adjusted to pH 9-10 with 10% aqueous Na_2CO_3. This mixture was washed with Et_2O, cooled and adjusted to pH 3-4 with cold dilute hydrochloric acid. The residual Et_2O was removed under a stream of nitrogen and the resulting solid was collected by filtration, washed with water, dried and crystallized from EtOH (Darco) to give 0.49 g of **204**, mp 171-172°C (lit.[14] mp 169-171°C): ^{1}H NMR[300 MHz, $(CD_3)_2SO$] δ 6.36 (d, 1H), 7.20 (d, 1h), 7.69 (dd, 1H), 7.81 (m, 1H), 7.91 (m, 1H), 8.22 (d, 1H), 13.33 (s, 1H); MS (ESI+) m/z 223.1 ($M+H^+$); MS (ESI-) m/z 219.9 (M-H).

Step 2:



A stirred mixture of **204** (0.29 g, 1.3 mmol) and DMF (5 ml), under nitrogen, was treated with EDC (0.25 g, 1.3 mmol) and HOBT (0.17 g, 1.3 mmol), kept at ambient temperature for 2 min and treated with **17b** (0.436 g, 1.29 mmol). It was kept at ambient temperature for 1 h and concentrated *in vacuo*. The residue was kept under a stream of nitrogen for 18 h and then chromatographed on silica gel with 5% MeOH-CH_2Cl_2. Crystallization of the product from EtOAc gave 0.36 g of **205**: MS (ESI+) m/z 540.1 ($M+H^+$), 562.1 ($M+Na^+$); MS (ESI-) m/z 538.0 (M-H), 574.0 (M+Cl), 584.0 ($M+CHO_2$).

Step 3:

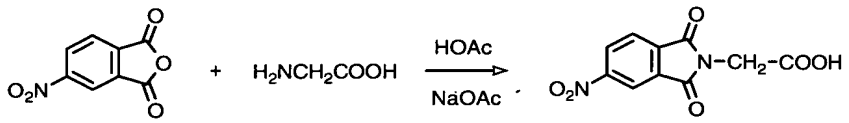


A mixture of **205** (1.18 g, 2.18 mmol), 50% MeOH-CH_2Cl_2 and 10% palladium-on-carbon catalyst was hydrogenated at an initial pressure of 40 psi for 2.25 h and

filtered. The solid was washed with 50% MeOH-CH_2Cl_2 and the filtrate was concentrated to give 0.92 g, of **203**. A sample which was chromatographed on silica gel with 5% MeOH-0.2% NH_4OH-CH_2Cl_2 and crystallized from MeOH had: MS (ESI+) m/z 512.4 ($M+H^+$), 534.3 ($M+Na^+$); MS (ESI-) m/z 510.3 (M-H), 546.2 (M+Cl); IR (drift) 3455, 3340, 3287, 1744, 1644, 1638 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{31}FN_5O_5$ ($M+H^+$) 512.2309, found 512.2308.

Example 70: N-{[(5*S*)-3-(4-{4-[(5-Amino-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide 208.

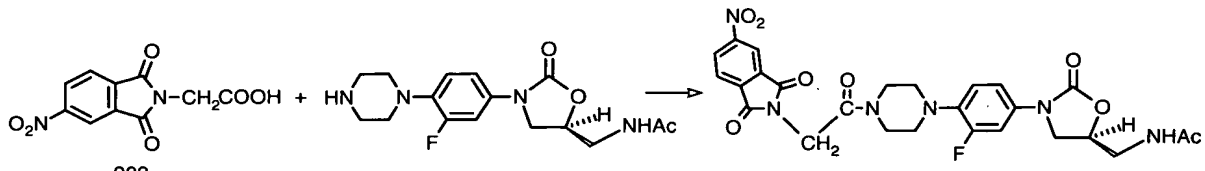
Step 1:



209

A stirred mixture of 4-nitrophthalic anhydride (1.4 g, 0.0072 mol), glycine (0.55 g, 0.0073 mol), sodium acetate (0.66 g, 0.0080 mol) and acetic acid (10 ml) was immersed in a bath that had been preheated to 100°C, warmed to 130°C and kept at that temperature for 90 min. It was then kept at ambient temperature for 3 h and the thick suspension was diluted with EtOH and filtered. The solid was washed with EtOH and then crystallized from EtOH to give 2.16 g of **209**: MS (ESI-) m/z 249.1 (M-H).

Step 2:

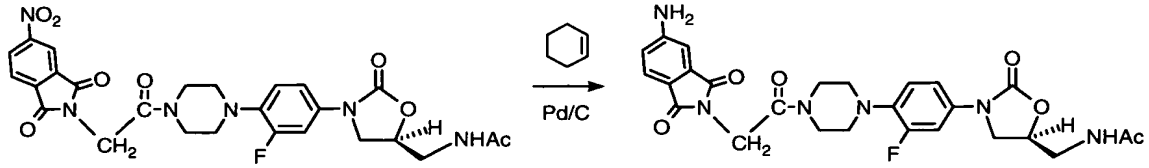


209 17b 210

A stirred mixture of **209** (0.25 g, 1.0 mmol) and pyridine (7 ml), under nitrogen, was treated with **17b** (0.34 g, 1.0 mmol), EDC (0.3 g, 1.6 mmol) and DMAP (10 mg), kept at ambient temperature for 3 h and concentrated *in vacuo*. Chromatography of the

residue on silica gel with 5% MeOH-CH_2Cl_2 gave 0.22 g of **210**: MS (ESI+) m/z 591.3 ($M+Na^+$); MS (ESI-) m/z 568.2 (M-H), 603.2 (M+Cl).

Step 3:

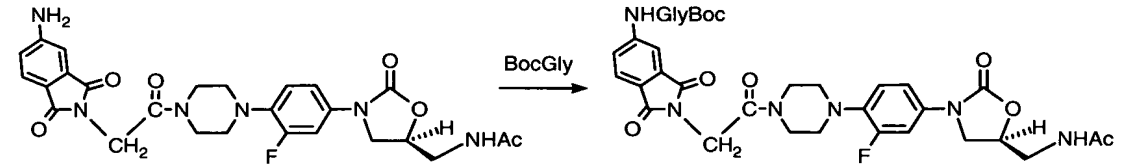


210 208

A stirred mixture of **210** (0.5 g, 0.88 mmol), ethanol (20 ml), cyclohexene (1 ml) and 10% palladium-on-carbon catalyst (0.12 g) was refluxed, under nitrogen, for 3.5 h, diluted with CH_2Cl_2 and filtered through celite. The filtrate was concentrated *in vacuo* to give 0.42 g of product. A sample of this material was crystallized from MeOH-EtOAc-hexane to give **208**: mp 241-243°C (dec); MS (ESI+) m/z 539.3 ($M+H^+$), 561.2 ($M+Na^+$); MS (ESI-) m/z 537.2 (M-H), 573.2 (M+Cl); IR (drift) 3421, 3382, 3364, 3341, 3234, 1763, 1743, 1701, 1661 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{28}FN_6O_6$ ($M+H^+$) 539.2054, found 539.2071.

Example 71: N^1-(2-{2-[4-(4-{(5*S*)-5-[(Acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-2-oxoethyl}-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)glycinamide (210).

Step 1:

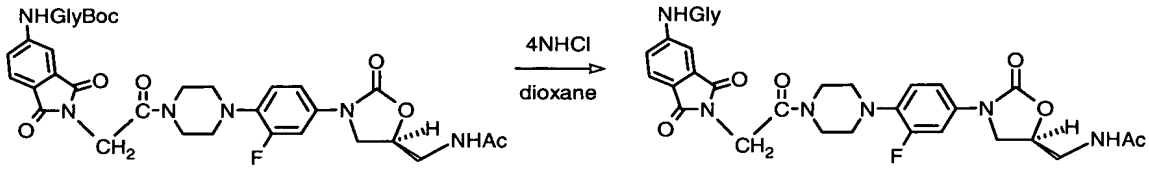


208 211

A stirred mixture of **208** (0.42 g, 0.78 mmol), N-Boc glycine (0.143 g, 0.817 mmol) and pyridine (6 ml), under nitrogen, was treated with EDC (0.22 g, 1.15 mmol) and DMAP (10 mg), kept at ambient temperature for 2 h 35 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-CH_2Cl_2 gave 0.4 g of **211**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.05 (s, 3H), 3.15, 3.24 (s, s, 4H), 3.70 (m, 2H), 3.80 (m, 3H), 3.89 (s, 2H), 3.94 (d, 2H), 4.06 (t, 1H), 4.56 (s, 2H),

4.82 (m, 1H), 5.42 (m, 1H), 6.44 (t, 1H), 7.10 (m, 2H), 7.50 (d, 1H), 7.61 (d, 1H), 7.77 (d, 1H), 7.93 (s, 1H), 9.45 (s, 1H); MS (ESI+) m/z 696.3 ($M+H^+$), 718.3 ($M+Na^+$); MS (ESI-) m/z 694.2 (M-H), 730.1 (M+Cl).

Step 2:

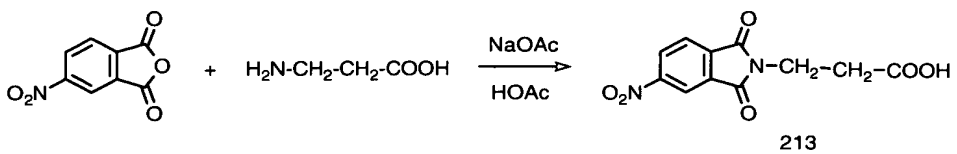


211 210

A sample of **211** (0.4 g, 0.57 mmol) was cooled in an ice bath, under nitrogen and, with stirring, treated, dropwise, with 4N hydrogen chloride in dioxane (3.5 ml). It was kept in the ice bath for 30 min and at ambient temperature for 3 h and the concentrated under a stream of nitrogen. The residue was mixed with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water and brine and concentrated. Chromatography of the residue on silica gel with 6% MeOH-0.3% NH_4OH-CH_2Cl_2 to 10% MeOH-0.5% NH_4OH-CH_2Cl_2 and crystallization of the product from MeOH gave 0.133 g of **210**: mp 153°C (dec); ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 1.84 (s, 3H), 2.96, 3.06 (s, s, 4H), 3.17 (s, 1.5H, MeOH), 3.38 (s, 2H), 3.41 (t, 2H), 3.61 (s, 2H), 3.72 (m, 3H), 4.10 (t, 1H), 4.10 (0.5H), 4.56 (s, 2H), 4.72 (m, 1H), 5.09 (broad s, 1H), 7.11 (t, 1H), 7.18 (dd, 1H), 7.52 (dd, 1H), 7.87 (d, 1H), 7.97 (dd, 1H), 8.24 (t, 1H), 8.32 (d, 1H); IR (drift) 3369, 3300, 3217, 1758, 1744, 1714, 1712, 1662, 1646 cm^{-1}; MS (ESI+) m/z 596.3 ($M+H^+$); MS (ESI-) m/z 630.1 (M+Cl). Anal. calcd for $C_{28}H_{30}FN_7O_7 \cdot CH_3OH$: C, 55.49; H, 5.46; N, 15.62. Found: C, 55.33; H, 5.44; N, 15.93.

Example 72: N^1-[2-(3-{4-[4-((5*S*)-5-{[(2,2-Difluoroethanethiolyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]piperazin-1-yl}-3-oxopropyl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl) glycinamide 212.

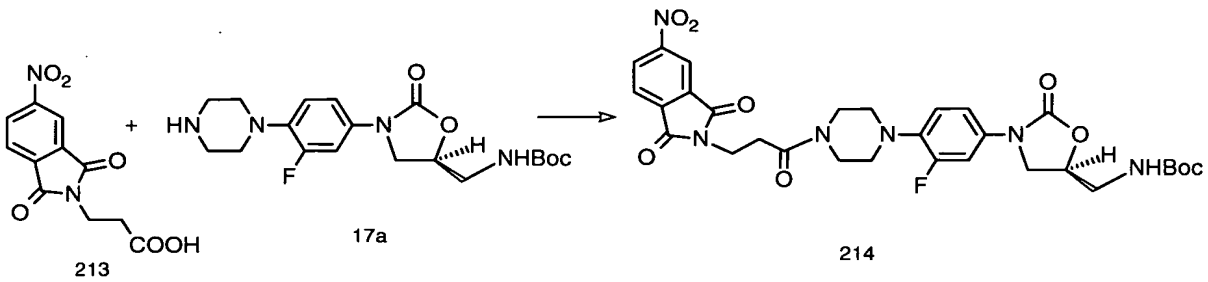
Step 1:



213

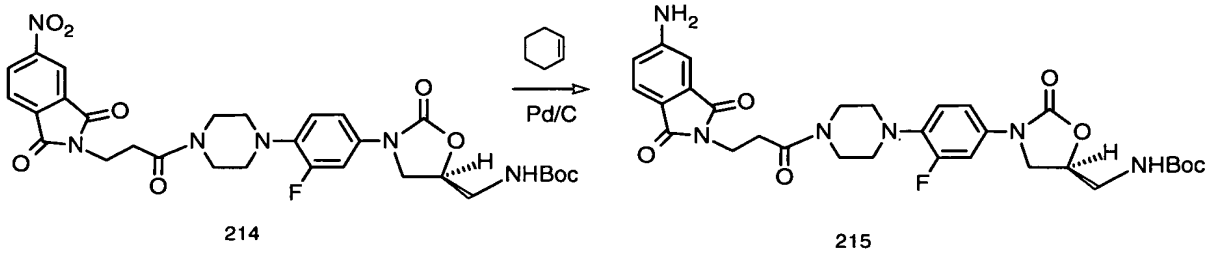
A stirred mixture of 4-nitrophthalic anhydride (2.8 g, 0.0145 mol), β-alanine (1.3 g, 0.0146 mol), sodium acetate (1.32 g, 0.0161 mol) and acetic acid (20 ml) was warmed, under nitrogen to 135°C during 90 min, kept at this temperature for 2 h and cooled to ambient temperature. It was mixed with EtOH (50 ml) and the solid was collected by filtration, washed with EtOH and dried at 55-60°C *in vacuo*. Crystallization from acetonitrile gave 2.34 g, mp 210-211°C and 0.27 g, mp 208-209°C of **213**: ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 2.64 (t, 2H), 3.83 (t, 2H), 8.13 (d, 1H), 8.50 (d, 1H), 8.62 (dd, 1H), 12.44 (s, 1H); MS (ESI+) m/z 287.1 ($M+Na^+$); MS (ESI-) m/z 263.1 (M-H).

Step 2:



A stirred mixture of **213** (1.17 g, 4.43 mmol) and pyridine (20 ml), under nitrogen was treated with EDC (1.27 g, 6.62 mmol), **17a**[5] (1.75 g, 4.44 mmol) and DMAP (20 mg), kept at ambient temperature for 19 h and concentrated *in vacuo*. A mixture of the residue and water was extracted with EtOAc and CH_2Cl_2. The extracts were washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 2% MeOH-CH_2Cl_2 gave 2.02 g of **214**: MS (ESI+) m/z 641.5 ($M+H^+$), 663.5 ($M+Na^+$); MS (ESI-) m/z 639.3 (M-H), 671.4 ($M+CH_3O$), 675.3 (M+Cl).

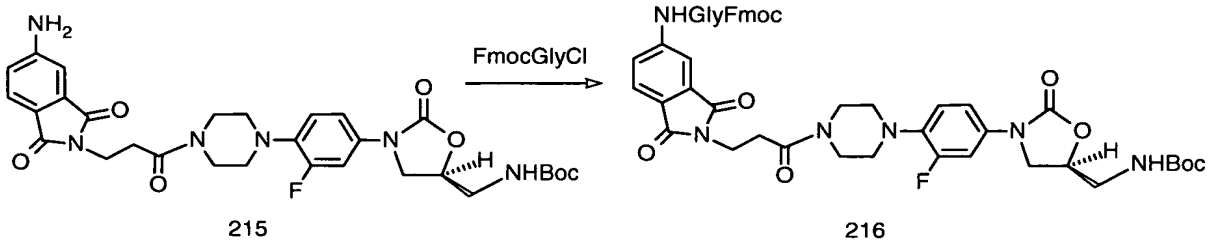
Step 3:



214 215

A stirred mixture of **214** (1.0 g, 1.56 mmol), cyclohexene (1.8 ml), 10% palladium-on-carbon catalyst (0.21 g) and EtOH (40 ml) was refluxed, under nitrogen for 3.25 h, cooled, diluted with CH_2Cl_2 and filtered through celite. The solid was washed with 20% EtOH-CH_2Cl_2 and the filtrates were concentrated. The residue was combined with the crude product from a second identical reaction and chromatographed on silica gel with 5% MeOH-CH_2Cl_2 to give 1.66 g of **215**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.80 (t, 2H), 3.04 (m, 4H), 3.55 (m, 2H), 3.65, 3.81 (m, m, 4H), 3.85 (m, 1H), 4.04 (m, 3H), 4.43 (s, 2H), 4.79 (m, 1H), 5.03 (m, 1H), 6.85 (dd, 1H), 6.92 (t, 1H), 7.06 (d, 1H), 7.12 (dd, 1H), 7.48 (dd, 1H), 7.63 (d, 1H); MS (ESI+) m/z 611 ($M+H^+$), 633.5 ($M+Na^+$); MS (ESI-) m/z 609.3 (M-H), 645.3 (M+Cl).

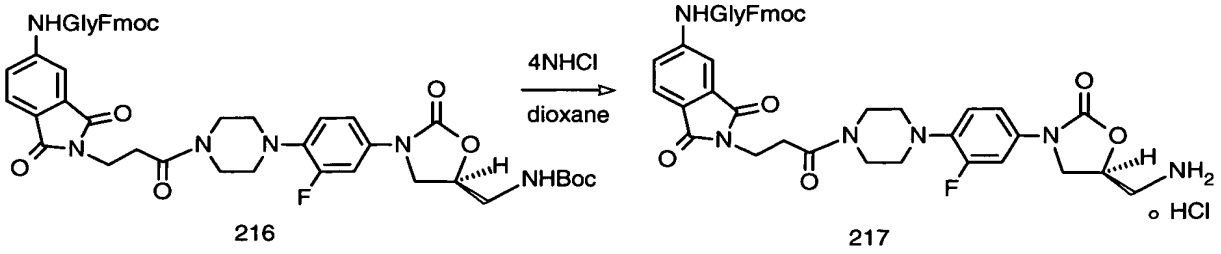
Step 4:



215 216

A stirred mixture of **215** (0.31 g, 0.507 mmol) and N-Fmoc glycyl chloride (0.167 g, 0.529 mmol) in THF (30 ml) was refluxed, under nitrogen for 3.5 h, cooled and concentrated *in vacuo*. Crystallization of the residue from MeOH-EtOAc gave 0.41 g of **216**: mp 175-177°C (dec); MS (ESI-) m/z 888.5 (M-H), 924.4 (M+35).

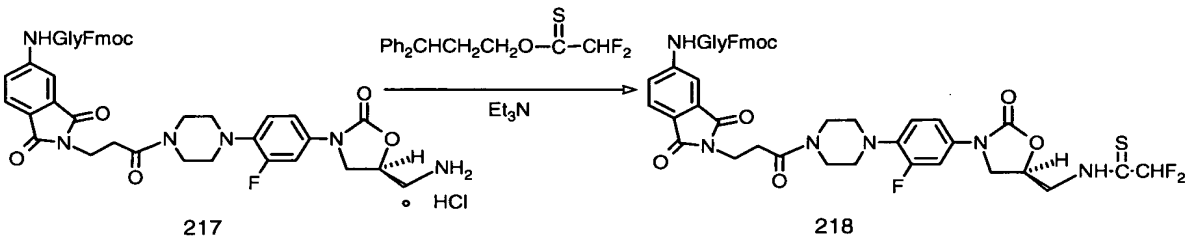
Step 5:



216 217

A sample of 216 (0.77 g, 0.866 mmol) was cooled in an ice bath under nitrogen and treated, dropwise with stirring during 1.5 min, with 4N hydrogen chloride in dioxane (7 ml). It was kept in the ice bath for 40 min and at ambient temperature for 110 min. Excess hydrogen chloride was removed with a stream of nitrogen and the resulting mixture was concentrated *in vacuo* to give 0.71 g of 217.

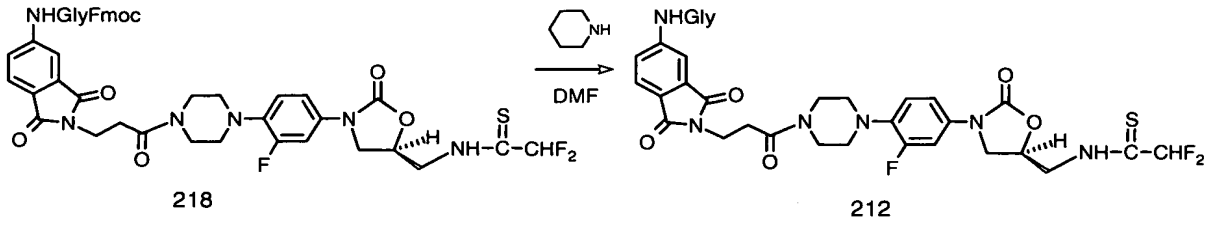
Step 6:



217 218

A stirred mixture of 217 (0.32 g) and triethylamine (0.11 ml) in CH_2Cl_2 (30 ml), under nitrogen was treated, dropwise, with a solution of O-(3,3-diphenylpropyl) difluoroethanethioate (0.15 g, 0.49 mmol) in CH_2Cl_2 (2 ml) and kept at ambient temperature for 4.5 h. Additional O-(3,3-diphenylpropyl) difluoroethanethioate (0.05 g) in CH_2Cl_2 (1 ml) was added and the mixture was kept at ambient temperature for 18 h and concentrated *in vacuo*. The residue was triturated with 3% MeOH-CH_2Cl_2 to give 0.27 g of 218: MS (ESI-) m/z 918.4 (M+Cl).

Step 7:



218 212

A stirred mixture of 14 (0.26 g, 0.294 mmol) in DMF (2 ml), under nitrogen, was treated with piperidine (0.06 ml), kept at ambient temperature for 30 min and concentrated *in vacuo*. Chromatography of the residue on silica gel with 5% MeOH-0.3% NH_4OH-CH_2Cl_2 to 7.5% MeOH-0.5% NH_4OH-CH_2Cl_2 gave 0.032 g of 101: MS (ESI+) m/z 662.3 ($M+H^+$); MS (ESI-) m/z 696.3 (M+Cl); IR (drift) 3241, 1749, 1744, 1710, 1677, 1663, 1645, 1628; HRMS calcd for $C_{29}H_{31}F_3N_7O_6S$ ($M+H^+$) 662.2008, found 662.2029.

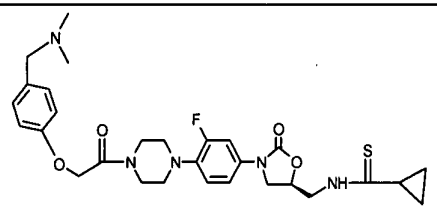
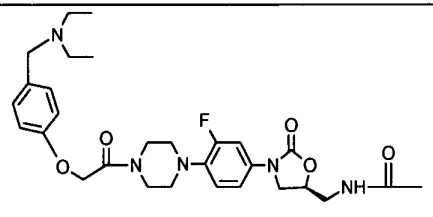
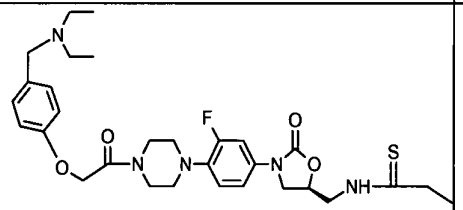
Example 73: MIC Test Method.

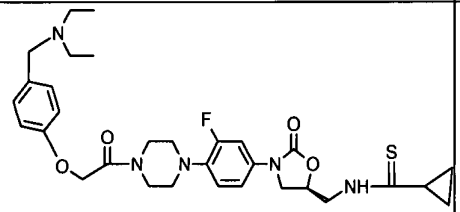
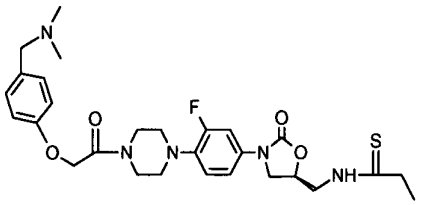
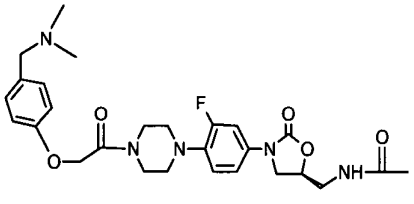
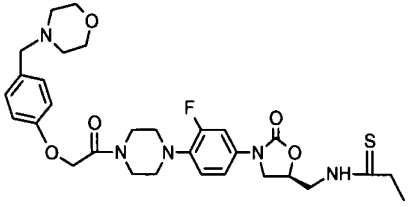
The *in vitro* MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog was prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug was added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar was mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to inoculation.

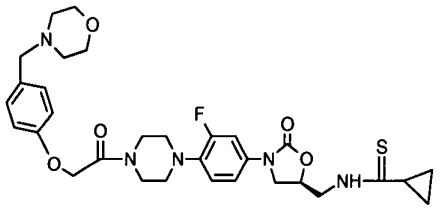
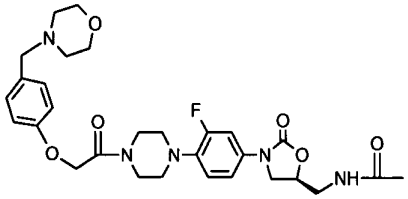
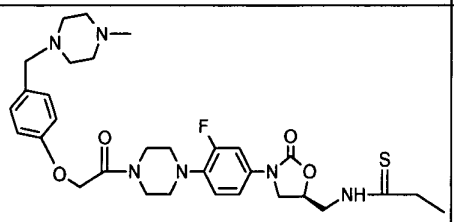
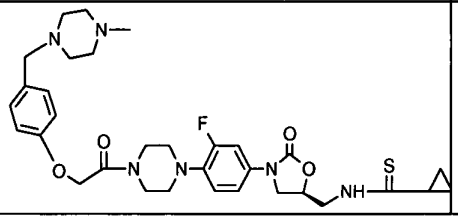
Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension was made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

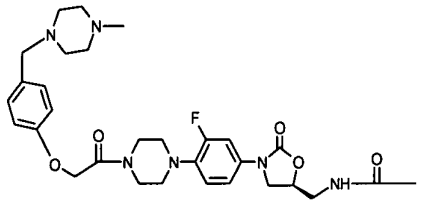
Following incubation the Minimum Inhibitory Concentration (MIC μg/ml), the lowest concentration of drug that inhibits visible growth of the organism, was read and recorded. The data is shown in Table I.

Table 1. **MIC Data**[a]

Compound No.	Structure	SAUR[b] 9213	SAUR 31583	SEPI[c] 30593	EFAE[d] 9217	EFAE[e] 12712	SPNE[f] 9912	SPYO[g] 152	HINF[h] 30063	HINF 31810	MCAT[i] 30607
2		2	4	1	1	1	0.125	0.125	16	8	2
8		32	> 64	8	32	32	2	2	> 64	> 64	32
9		4	32	2	2	2	0.25	0.25	32	32	4

Compound No.	Structure	SAUR[b] 9213	SAUR 31583	SEPI[c] 30593	EFAE[d] 9217	EFAE[c] 12712	SPNE[f] 9912	SPYO[g] 152	HINF[h] 30063	HINF 31810	MCAT[i] 30607
10		2	8	1	2	2	0.25	0.25	32	32	2
13		8	16	1	1	2	0.125	0.25	16	16	4
14		16	> 64	8	8	8	0.5	0.5	64	32	32
17		8	32	2	1	2	0.25	0.5	64	32	4

Compound No.	Structure	SAUR[b] 9213	SAUR 31583	SEPI[c] 30593	EFAE[d] 9217	EFAE[c] 12712	SPNE[f] 9912	SPYO[g] 152	HINF[h] 30063	HINF 31810	MCAT[i] 30607
18		4	16	1	1	2	0.25	0.25	64	32	2
19		16	> 64	8	4	8	1	1	> 64	64	64
22		8	32	2		2	0.125	0.25	32	16	2
23		16	> 64	8		8	0.5	0.5	64	64	32

Compound No.	Structure	SAUR[b] 9213	SAUR 31583	SEPI[c] 30593	EFAE[d] 9217	EFAE[e] 12712	SPNE[f] 9912	SPYO[g] 152	HINF[h] 30063	HINF 31810	MCAT[i] 30607
24		4	16	2		2	0.125	0.25	32	16	2

[a] Minimum inhibitory concentration (μg/mL).

[b] *S. aureus*

[c] *S. epidermidis*

[d] *E. Faecalis*

[e] *E. Faecium*

[f] *S. pneumonia*

[g] *S. pyogenes*

[b] *H. influenzae*

[i] ***M. catarrhalis***